ORIGINAL ARTICLE

Risk of cutaneous squamous cell carcinoma after treatment of basal cell carcinoma with vismodegib

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Background: Vismodegib is a first-in-class agent targeting the hedgehog signaling pathway for treatment of patients with locally advanced basal cell carcinoma (BCC) and metastatic BCC. There have been concerns about the development of squamous cell carcinoma (SCC) in patients treated with this drug.

Objective: We sought to determine whether treatment with vismodegib is associated with an increase in the risk of cutaneous SCC.

Methods: In this retrospective cohort study, patients treated with vismodegib as part of phase I and II clinical studies were compared with participants from the University of California, San Francisco, Nonmelanoma Skin Cancer Cohort who received standard therapy for primary BCC. In total, 1675 patients were included in the analysis, and the development of SCC after vismodegib exposure was assessed.

Results: The use of vismodegib was not associated with an increased risk of subsequent development of SCC (adjusted hazard ratio, 0.57; 95% confidence interval, 0.28-1.16). Covariates including age, sex, history of previous nonmelanoma skin cancer, and number of visits per year were significantly associated with the development of SCC.

Limitations: A limitation of the study was that a historic control cohort was used as a comparator.

Conclusions: Vismodegib was not associated with an increased risk of subsequent SCC when compared with standard surgical treatment of BCC. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.03.038.)

Key words: basal cell carcinoma; locally advanced; metastatic; safety; squamous cell carcinoma; vismodegib.

Basal cell carcinoma (BCC) is the most common form of nonmelanoma skin cancer (NMSC) in the United States. In 2012, there were an estimated 726,000 people in the United States treated for 1.03 million BCCs.[1] Although most of these tumors are amenable to surgical or radiation treatment, locally advanced BCC (laBCC) and metastatic BCC (mBCC) represent a special subset that cannot easily be treated with these standard methods.[2] Locally advanced BCC and mBCC are thought to represent roughly 1% to 10% of all BCCs, with mBCCs accounting for 0.0028% to 0.5%.[3]

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Conflicts of interest: Dr Chren was a consultant for Genentech from 2012-2013 for patient-reported outcomes. Drs Caro, Sadetsky, Sima, and Hou are employees of Genentech/Roche and hold stock and stock options in Genentech/Roche. Dr Arron has been an investigator on Genentech clinical trials related to vismodegib. The remaining authors have nothing to disclose.

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Vismodegib has become a new treatment option for this subset of patients.[4,5] Vismodegib, a first-in-class agent that targets the hedgehog signaling pathway, has become a new treatment option for this subset of patients.[6-9] Its efficacy was proven in the pivotal study (ERIVANCE), with response rates of 30.3% in metastatic disease and 42.9% in locally advanced disease.[2,5,10,11]

Despite the clinical efficacy and reported safety profiles of vismodegib, there have been some concerns about the development of squamous cell carcinoma (SCC) in patients being treated with this drug.[12-15] Also, a recently published retrospective analysis by Mohan et al[16] demonstrated an increased risk of cutaneous SCC after therapy.[16]

Because of the lack of treatment options for inoperable and nonradiatable BCC, vismodegib was approved by the US Food and Drug Administration in a pivotal phase 2 trial without a placebo arm, making it difficult to assess whether the incidence of observed SCC would have been different when compared with a placebo-controlled group. Vismodegib has also been studied in a phase 2 trial as maintenance therapy in ovarian cancer, and no increased incidence of SCC was reported when compared with the placebo-controlled arm.[17] However, duration of vismodegib exposure in the ovarian study was approximately 5 months. Therefore, larger studies with longer-term treatment and follow-up are needed. Although there is no clear molecular mechanism for the development of SCC associated with hedgehog pathway inhibition, current concerns are that other targeted molecular inhibitors, such as BRAF and γ-secretase inhibitors may drive secondary SCC.[14,15] The coexistence of BCC and SCC in the same patients is not unexpected. Host and host risk factors are generally shared for both SCC and BCC, which suggests a common underlying predisposition for development of NMSC.[18] In a medulloblastoma model, hedgehog pathway inhibition was shown to activate the RAS/MAPK pathway.[19] It has also been proposed that in a mouse model, PTCH may be critical in determining basal or squamous cell lineage and that both tumor types may arise from the same target cell, depending on host and carcinogenic factors.[20] However, there are no data in human disease to support these proposals. To counsel and screen patients taking this medication, it is of clinical importance to determine whether vismodegib increases the risk of SCC.

To accomplish this, our group compared pooled outcome data from patients treated with vismodegib as part of completed and ongoing phase I and phase II clinical studies with data from the UCSF Nonmelanoma Skin Cancer Cohort study of patients treated for primary BCC with standard therapy.[21] Using these 2 cohorts, we aimed to determine whether treatment with vismodegib is associated with an increase in the risk of cutaneous SCC.

CAPSULE SUMMARY

- There have been concerns about the development of squamous cell carcinoma in basal cell carcinoma patients treated with vismodegib.
- In this retrospective cohort study, vismodegib was not associated with an increased risk of subsequent squamous cell carcinoma.
- Concerns about the development of squamous cell carcinoma in vismodegib-treated patients do not appear to be warranted.

METHODS

Vismodegib-treated group

Patients treated with vismodegib as part of 2 phase II (STEVIE and ERIVANCE) and 2 phase I clinical trials were included in this study. The design of these trials ensured that none of the patients enrolled could have prior treatment with vismodegib, and therefore each patient was mutually exclusive and counted only once.

STEVIE is an open-label, noncomparative, multicenter, phase II trial of vismodegib in patients with locally advanced or metastatic BCC who were otherwise without satisfactory treatment options. Patients received vismodegib in 150-mg oral capsules once a day on a continuous basis until the development of progressive disease, unacceptable toxicity, consent withdrawal, or death. Between June 2011 and November 2013 (the cutoff date for this interim analysis), 501 patients (mBCC, n = 31; laBCC n = 470) were enrolled in this trial. Median duration of vismodegib exposure was 36.4 weeks. From the STEVIE cohort, only 4 patients of 501 total patients were lost to follow-up.[22]

ERIVANCE is a pivotal, phase II, single-arm, multicenter clinical trial that enrolled patients with locally advanced or metastatic BCC who had inoperable disease or for whom surgery was inappropriate. All enrolled patients received oral 150 mg/day vismodegib until disease progression, intolerable toxicity, or withdrawal from the study. A total of 104 patients (mBCC, n = 33; laBCC, n = 71) were enrolled between February 2009 and November 2010. From the ERIVANCE cohort, only 3 patients of 104 total patients were lost to follow-up.[2,11]

Abbreviations used:

BCC: basal cell carcinoma
BCNS: basal cell nevus syndrome
laBCC: locally advanced basal cell carcinoma
mBCC: metastatic basal cell carcinoma
NMSC: nonmelanoma skin cancer
SCC: squamous cell carcinoma

Additionally, 2 phase I clinical trials, including 33 patients with laBCC (n = 15) or mBCC (n = 18), treated with vismodegib, also contributed data to this study. All patients had follow-up data.[23]

University of California, San Francisco, NMSC cohort

For the surrogate placebo cohort, we used data from a prospective cohort study of consecutive patients treated with standard therapy between 1999-2000 for primary nonmelanoma skin cancer at the University of California, San Francisco Medical Center, and the San Francisco Veterans Affairs Medical Center.[21] This study enrolled 1253 eligible patients, with 1585 primary NMSCs treated with destruction, excision, or Mohs surgery. Follow-up information was available for 1174 patients with 1488 tumors for up to 10 years. Only patients with primary BCC as the index tumor at enrollment were included in this analysis, for a total number of 1119 patients and tumors. No patients in this cohort had mBCC.

Statistical analysis

Baseline demographic characteristics were assessed for both cohorts at the time of treatment of BCC and were analyzed with the use of descriptive statistics. Means and standard deviations were used for continuous variables, and percentages were used for categorical variables. Because the dataset of patients treated surgically did not include metastatic cases, patients with mBCC in the vismodegib group were excluded from this analysis because of lack of data in the comparator group.

Standardized incidence ratios were calculated for diagnosis of SCC 1 year after treatment started (vismodegib treatment and surgery, respectively), with vismodegib-treated patients as the exposed group. Relative risks were also calculated for clinical variables of age, sex, ethnicity, and basal cell nevus syndrome (BCBS).

Cox proportional hazards models were used to estimate hazard ratios and their 95% confidence intervals to assess the association between treatment with vismodegib and the development of SCC. The event of interest was diagnosis of SCC, and the follow-up was censored at the earliest of death or end of observation period. Age and sex were included in the model as covariates a priori, given the known association of these factors and SCC risk. The average number of dermatologist visits per year was also included a priori because this was known to be different between the 2 groups. The other covariates considered were race, history of NMSC, diagnosis of BCNS, and latency time between diagnosis of BCC and initiation of the standard surgical treatment or vismodegib. Of these, race, BCNS, and latency time were removed through a modified Allan-Cady backwards selection procedure, with a threshold value of $P < .05$ required for retention in the model. Only previous history of NMSC was significant. Further sensitivity analyses were performed by use of the removed predictors (race, BCNS, and latency times) individually, with no change in the outcome. Therefore, these variables were not included in the final model. Binary tests of interaction were performed between all included predictors (data not shown). The proportional hazards assumption was tested and confirmed with the Schoenfeld test. Stata, version 13 (StataCorp, College Station, TX) software, was used for all statistical analyses.

Institutional review board approval

Appropriate institutional review board approval at the University of California, San Francisco, was obtained for this study.

RESULTS

In total, 1675 patients were included in the analysis (556 in the vismodegib-treated cohort and 1119 in the comparator cohort). The demographic characteristics for the study populations are presented in Table I. There was a greater proportion of patients with BCNS in the vismodegib-treated cohort (13.9% vs 0.8%). Patients in the vismodegib-treated group were followed for a shorter period of time compared with the comparator cohort (mean, 1.1 years vs 4.8 years, respectively), but the vismodegib-treated patients were seen more frequently than the comparator cohort were seen (12 vs 1.9 visits/year, respectively) during the follow-up period. Finally, patients treated with vismodegib had a longer latency time from diagnosis of BCC to initiation of treatment (mean, 12.5 years vs 0.14 years). The 1-year end point was analyzed, and the results were found. At the end of 1 year after treatment initiation, 5% of vismodegib-treated patients and 4% of patients treated with standard therapy had development of SCC ($P = .34$).

The standardized incidence ratio for SCC at 1 year in the vismodegib-treated group compared with the standard treatment cohort was 1.3 (95% confidence

Table I. Population demographics

Characteristic	All patients (n = 1675)	Vismodegib-treated (n = 556)	Nonexposed, University of California, San Francisco (n = 1119)	*P* value
Male sex, n (%)	1115 (66.6)	330 (59.4)	785 (70.2)	<.001
White race, n (%)	990 (59.1)	378 (68.0)	631 (56.4)	<.001
Age at BCC treatment, mean (SD), years	66 (16)	66 (17)	65 (15)	.35
Age at BCC treatment >60 years, n (%)	1066 (63.6)	368 (66.2)	698 (62.4)	.13
History of nonmelanoma skin cancer, n (%)	681 (40.1)	61 (11.0)	620 (55.4)	<.001
Basal cell nevus syndrome, n (%)	86 (5.1)	77 (13.9)	9 (0.8)	<.001
Latency time from BCC diagnosis to treatment, mean (SD), years	4.2 (9)	12.5 (11.9)	0.1 (0.2)	<.001
Clinical follow-up, mean (SD), y	3.6 (3.3)	1.1 (0.8)	4.8 (3.5)	<.001
Office visits per year, mean (SD), n	5.5 (5.2)	12	1.9 (2.3)	<.001
Patients with subsequent squamous cell carcinoma, n (%)	291 (17.4)	32 (5.8)	259 (23.2)	<.001
Patients with subsequent squamous cell carcinoma at 1 year, n (%)	73 (4.4)	28 (5.0)	45 (4.0)	.34

BCC, Basal cell carcinoma; *SD*, standard deviation.

interval, 0.8-2.1). None of these incidence ratios stratified by demographic variables showed a statistically higher incidence of SCC when comparing treatment with vismodegib with standard treatment of BCC.

Our multivariate proportional hazards analysis demonstrated that use of vismodegib was not associated with an increased risk of subsequent development of SCC (adjusted hazard ratio, 0.57; 95% confidence interval, 0.28-1.16). Other covariates with expected associations of increased SCC risk such as age, sex, history of previous NMSC, and number of visits per year were statistically significantly associated with the development of SCC (Table II).

Because patients in clinical trials undergo more rigorous follow-up, we explored collinearity between type of treatment and average number of visits per year by undertaking sensitivity analysis. We compared effect sizes both with and without the number of visits per year included in the model, with no change in outcome. We also included the variable as a time-varying covariate, with similar results. Therefore, in the final model, average number of visits per year was included.

In addition, because the presence of BCNS is an important factor for patients with BCC, sensitivity analysis including this covariate was performed. There was a significant change in the effect size, probably because of the small number of patients, resulting in an unstable model. Thus, this covariate could not be included.

DISCUSSION

This study aimed to investigate the clinical concern for subsequent SCC in patients treated with vismodegib.[12-15] Our analysis demonstrated that vismodegib was not associated with an increased incidence of SCC diagnosed within 1 year after treatment. Moreover, multivariate analysis also demonstrated no long-term increased risk of SCC in patients treated with vismodegib when compared with patients treated with standard surgical treatment. In this analysis, factors known to be associated with development of SCC, such as age, sex, history of NMSC, and number of visits per year, continued to be significant predictors for the development of SCC in this study population.

A recently published retrospective analysis by Mohan et al[15] demonstrated a significantly increased risk of SCC after vismodegib therapy, with a hazard ratio of 8.12. These discordant results may be due to important differences in study design. First, the frequency of evaluation by a dermatologist is an important confounder in cancer-screening studies. Several studies demonstrated that an increase in screening for skin cancer results in a higher likelihood of detecting tumors and, as a consequence, an increased incidence of NMSC.[18,24] In a nationwide skin cancer—screening study, Eisemann et al[25] demonstrated that the implementation of standardized screening for NMSC increased the incidence of NMSC by 47% in women and 34% in men. Mohan et al[26] did not include or control for frequency of follow-up in their analysis. Patients treated with vismodegib, particularly those enrolled in clinical trials before the 2012 approval of this medication, are screened more frequently than the average standard of care. This has the potential to introduce both over-diagnosis and lead time bias in the diagnosis of SCC. Therefore, it is quite possible that the close

Table II. Multivariate Cox proportional hazards model

Characteristic All patients (n = 1675)	Hazard ratio (95% confidence interval)	*P* value
Treatment with vismodegib (yes vs no)	0.57 (0.28-1.16)	.122
Age at basal cell carcinoma treatment (>60 vs ≤60 years)	2.96 (2.17-4.03)	<.001
Sex (male vs female)	1.79 (1.30-2.47)	<.001
History of nonmelanoma skin cancer (yes vs no)	1.66 (1.26-2.20)	<.001
Office visits per year	1.06 (1.01-1.11)	.009

follow-up and standardized skin cancer—screening of patients taking vismodegib have led to increased surveillance and thus increased SCC detection, rather than an actual increase in secondary cancer risk. Additionally, a recent editorial addressed the limitations of the Mohan study, calling for a trial design more consistent with our study design for accurate analysis.[27] Furthermore, 2 published comments addressed the concerns of the Mohan et al report, concluding that their study design and statistical analysis may be inadequate to support their findings.[28,29]

Second, our study defined entry time at the initiation of treatment rather than the diagnosis of BCC. We also analyzed age at treatment rather than age at diagnosis. A number of factors including patient denial, access to care, and logistic issues may lead to a delay between the diagnosis of skin cancer and eventual treatment (either with vismodegib or by surgery). As with any targeted molecular inhibitor, close surveillance and frequent skin checks are recommended. Although Mohan et al reported a latency period from BCC diagnosis to SCC diagnosis, they did not report or adjust for the latency between BCC diagnosis to initiation of treatment. Defining the entry time as the initiation of exposure and controlling for age at initiation of treatment rather than age at diagnosis is a more appropriate approach. In our population, the average latent time between diagnosis and treatment initiation was longer for the vismodegib-treated cohort, as expected. However, adjustment for this latency time did not affect the association between treatment and SCC.

Similarly, an average clinical follow-up time of 8.5 years is reported in the Mohan et al study, but it is unclear how much of that time is actually post-vismodegib exposure time.[26] Our data present a mean clinical follow-up time of 3.6 years, all clinically relevant time after vismodegib exposure.

There were several limitations to our study. We used a historic control cohort as a comparator because there was no matched placebo-controlled cohort in the vismodegib trials. In addition, patients in the vismodegib-treated cohort had laBCC not amenable to surgery, whereas our standard treatment group included patients with BCC who were amenable to destruction, excision, or Mohs surgery. Finally, SCC cases in the vismodegib-treated cohort were reported by the study physician, whereas in the standard treatment cohort, SCC diagnosis was obtained through chart review. We expect that reporting of SCC in the context of adverse event reporting in a clinical trial for skin cancer would be accurate. Furthermore, the inherent nature of a pooled data analysis from the ongoing vismodegib clinical trials potentially lends itself to Simpson's paradox, with differing results from the individual and pooled groups. We performed sensitivity analyses and found no difference between the individual and pooled groups.

Taken together, these data suggest that incident SCC risk in patients treated with vismodegib is a function of increased screening rather than a drug-specific effect.

CONCLUSIONS

On the basis of our findings, vismodegib was not associated with an increased risk of subsequent SCC when compared with standard surgical treatment of BCC. However, further large-scale, placebo-controlled trials are needed to definitively assess this risk.

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