




Vismodegib improves quality of life in patients with periocular locally advanced basal cell carcinoma: subgroup analysis, STEVIE trial

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Abstract

Objectives To evaluate the effect of locally advanced periocular basal cell carcinoma (POLA-BCC) on health-related quality of life (HRQoL) and the benefit of vismodegib treatment among participants in the Safety Events in Vismodegib (STEVIE) trial between 2011 and 2017.

Methods The STEVIE trial was conducted in patients with BCC (all anatomic locations) who were treated with vismodegib in 28-day cycles. Patients completed the Skindex-16, a validated questionnaire for the analysis symptoms, emotions, and functioning, at baseline, on day 1 of cycle 2, on day 1 of cycle 7, and at the end-of-study visit. For the present study, data mining techniques were used to construct an ophthalmic database of the STEVIE study. Skindex-16 scores were compared among patients with POLA-BCC between baseline and follow-up and between patients with POLA-BCC and patients with locally advanced BCC on other sites of the head and face (controls).

Results The cohort included 169 patients with POLA-BCC and 428 patients with non-periocular head BCC. Patients with POLA-BCC had a significantly worse overall functioning score at baseline than controls ($p = 0.038$) and a lower score specifically in activities of daily living ($p = 0.001$). At the last follow-up, patients with POLA-BCC showed significant improvement in scores for functioning (100%), symptoms (100%), and emotions (75%) relative to baseline.

Conclusions Secondary analysis of the results of the STEVIE trial showed that the HRQoL of patients with POLA-BCC is significantly impaired and can be greatly improved with vismodegib treatment.

Introduction

Basal cell carcinoma (BCC) is the most frequently diagnosed cancer worldwide. It affects an estimated two million

persons in the United States each year and the incidence is gradually increasing [1, 2].

Periocular BCC accounts for 4.4–18% of all BCCs and ~90% of all malignant periocular tumors [1, 3]. In most cases, it is characterized by local spread and a very low tendency to metastasize, and it can be cured by standard surgical interventions. However, a small minority of patients have periocular locally advanced BCC (POLA-BCC) for which surgical treatment is challenging. POLA-BCC may be associated with severe ocular morbidity and loss of vision or even loss of the eye and orbital contents [4, 5].

Health-related quality of life (HRQoL) is evolving as one of the most important treatment goals of modern medicine [6, 7]. Although BCC was originally considered to cause little handicap [8], recent studies reported that disease-related symptoms may affect HRQoL in terms of activities of daily living (ADL), emotional well-being, and social and leisure activities [9]. However, even though HRQoL has been investigated in patients with locally

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Table 1 Three domains of the Skindex-16.

Symptoms	Emotions	Functioning
1. Skin itching	5. Persistence or recurrence of condition	12. Effect of skin on interaction with others
2. Skin burning or stinging	6. Worry about condition	13. Effect of skin on desire to be with people
3. Skin hurting	7. Appearance of skin	14. Skin making it hard to show affection
4. Skin irritated	8. Frustration about skin	15. Effect of skin on daily activities
	9. Embarrassment about skin	16. Skin making it hard to work/have enjoyment
	10. Annoyed about skin	
	11. Feeling depressed	

advanced and metastatic BCC [9], there are no studies focusing on POLA-BCC.

Vismodegib (Erivedge®), a hedgehog signaling pathway inhibitor, is emerging as the treatment of choice for locally advanced BCC [10, 11]. The SafeTy Events in Vismodegib trial (STEVIE), a single-arm, multicentre, open-label study of the largest group of patients with locally advanced BCC to date, confirmed the safety and efficacy of vismodegib in a setting representative of clinical practice [12]. Further assessment of vismodegib in patients with POLA-BCC in the STEVIE study found that it was tolerable and effective, showing discontinuation of treatment due to adverse events in 23.8%, complete response in 28.7%, and partial response in 38.5% [13]. However, its effect on HRQoL specifically in patients with POLA-BCC has not been evaluated.

Studies have shown that the severe disfigurement associated with periocular conditions can cause high levels of psychosocial distress [14] and that blindness and low vision, which may be a consequence of POLA-BCC, can lead to depression and anxiety [15]. Prompted by these findings, we sought to evaluate the impact of POLA-BCC on HRQoL compared to non-periocular locally advanced head and facial BCC and to determine the benefit of vismodegib on HRQoL in this setting. Data for the study were derived from the STEVIE trial [9, 10].

Methods

STEVIE study

The STEVIE study investigated the safety and efficacy of vismodegib and its effect on HRQoL in patients with BCC treated at 167 sites in 36 countries between July 1, 2011 and June 14, 2017. The study methods and procedures have previously been described in detail [5, 12]. In brief, a single-arm, multicentre, open-label study design was used. Patients received 150 mg of oral vismodegib capsules once a day on a continuous basis in 28-day cycles until progressive

disease, toxicity, or withdrawal. HRQoL was evaluated with the Skindex-16, a dermatologic questionnaire with proven reliability and validity [16] covering three domains (Table 1): symptoms (four items), emotions (seven items), and functioning (five items), rated on a scale of 0 (never bothered) to 6 (always bothered). Patients completed the questionnaire before onset of vismodegib treatment (baseline), day 1 of cycle 2, day 1 of cycle 7, and at the end-of-study visit [9, 10]. Scores were aggregated and transformed to yield a maximal total score of 100, with higher scores signifying a greater adverse impact on HRQoL [9, 10].

Secondary analysis of STEVIE data

In the original STEVIE study, findings were analyzed for the cohort as a whole (BCC at any anatomic site) and did not distinguish ocular involvement as a defined tumor site or any other specific ocular consideration. Therefore, for the present study, data mining techniques were used to construct an ophthalmic database of the STEVIE study. Ophthalmic involvement was identified by a natural language processing search for anatomical ophthalmic keywords. All relevant tumor descriptions were evaluated by an experienced orbital surgeon. Scores on the Skindex-16, overall and by domain, were compared among patients with POLA-BCC between baseline and follow-up, and between patients with POLA-BCC and patients with locally advanced BCCs in other areas of the head and face (control group). In the POLA-BCC group, a secondary analysis was performed between patients who completed the treatment and those who terminated their treatment due to adverse events.

Statistical analysis

The relevant demographic and clinical data were compared using descriptive statistics. Analyses of covariance were used to assess the observed differences between groups. Mann–Whitney *U* test and Wilcoxon signed rank test were applied for paired samples. Chi-square or Fisher's exact test

Table 2 Baseline characteristics of study participants.

	Ocular BCC	Head BCC	<i>p</i>
<i>N</i>	169	428	
Age (yr), mean (SD)	68.82 (15.31)	67.28 (15.25)	0.314
Male, <i>n</i> (%)	100 (59.2)	251 (58.6)	0.927
Locally advanced BCC, <i>n</i> (%)	166 (98.2)	421 (98.4)	1
Metastatic BCC, <i>n</i> (%)	3 (1.8)	7 (1.6)	
Gorlin syndrome, <i>n</i> (%)	28 (16.6)	109 (25.5)	0.023
Histologically confirmed, <i>n</i> (%)	168 (99.4)	428 (100.0)	0.288
Time from initial diagnosis (yr), median (IQR)	7.76 (2.57, 17.58)	8.7 (2.46, 19.76)	0.717
Time from initial diagnosis of Gorlin syndrome (yr), median (IQR)	19.91 (9.72, 34.82)	21.95 (7.76, 33.68)	0.748
Measurable disease, <i>n</i> (%)	169 (100.0)	415 (97.0)	0.003

was used, as appropriate, for nominal variables. Multiple comparisons were adjusted with the Bonferroni correction. All statistical analyses were two-sided, and statistical significance was set at a *p* value of 0.05. Data were generated with Prism version 7 (GRAPHPAD Software Inc.) and R version 3.4.2 (R Development Core Team 2017).

Results

Patient population

Between July 1, 2011 and June 14, 2017, 1232 patients were enrolled in the STEVIE study. By study completion, 1215 patients had received at least one dose of vismodegib. HRQoL data were available for 169 patients with POLA-BCC and 428 patients with non-POLA-BCC in the head and face. Their clinical characteristics are shown in Table 2. There were no significant between-group differences in any of the parameters evaluated except measurable disease.

Overall Skindex-16 scores: differences between groups

The Skindex-16 results showed that POLA-BCC had a negative effect on HRQoL. The baseline median (range) overall score was 34 (15.5, 53) in the POLA-BCC group and 30 (12, 49) in the control group ($p = 0.1327$). Both groups demonstrated a meaningful improvement in overall HRQoL score after treatment. The respective end-of-study scores were 9 (0, 29.75, $p < 0.001$) and 11 (1, 33, $p < 0.001$), with a 10% greater overall improvement in the POLA-BCC group compared with the control one.

Skindex-16 scores over time: POLA-BCC group

An improvement in HRQoL scores were noted in the POLA-BCC group from baseline to the first day of the

second cycle of treatment in all major domains: symptoms [from 4 (0, 9) to 2 (0, 6), $p = 0.014$], emotions [from 22.5 (11, 33) to 12 (2.75, 24), $p < 0.001$], and functioning [from 6 (0, 16.5) to 2.5 (0, 12), $p < 0.001$]. The improvement continued to increase to the end of the study, to 100% for symptoms and functioning [from 6 (0, 17) to 0 (0, 9), $p = 0.003$ and from 4 (0, 9) to 0 (0, 5), $p < 0.001$, respectively] and to 75% for emotions [from 22 (11, 33) to 5.5 (0, 19.25), $p < 0.001$] (Fig. 1).

Forty-seven of the 169 POLA-BCC patients (27.8%) terminated their treatment due to adverse events. No statistically significant differences were observed between them and patients who completed the treatment, in all major domains (Table 3).

Skindex-16 domain scores: differences between groups

At baseline, there were no between-group differences in total score for the symptoms domain ($p = 0.979$) or in the individual scores for the four items addressing symptoms: skin itching, burning or stinging, hurting, and irritated (Fig. 2).

The total score for the functioning domain was significantly higher in the POLA-BCC group than the control group [6.00 (0.00, 17.00) vs 4.00 (0.00, 13.00), $p = 0.038$]. ADL accounted for the difference between the groups [1.00 (0.00, 4.00) vs 0.00 (0.00, 3.00), $p = 0.001$], with no significant differences in the other items addressing functioning: interactions with others ($p = 0.864$), desire to be with other people ($p = 0.221$), ability to show affection ($p = 0.357$), and ability to work or do enjoyable activities ($p = 0.115$).

In the emotions domain, there was no significant difference in total score between the groups ($p = 0.079$). Analysis by the individual items revealed that the patients with POLA-BCC were significantly more annoyed about their skin condition than the control patients [3.00 (0.00, 5.00) vs 3.00 (1.00, 6.00), $p = 0.049$]. There were no significant

Fig. 1 Change in scores on the Skindex-16 HRQoL subscales in patients with POLA-BCC.

A statistically significant improvement in HRQoL scores were noted from baseline to the first day of the second cycle of treatment in all major domains: Emotion, Functional and Symptom.

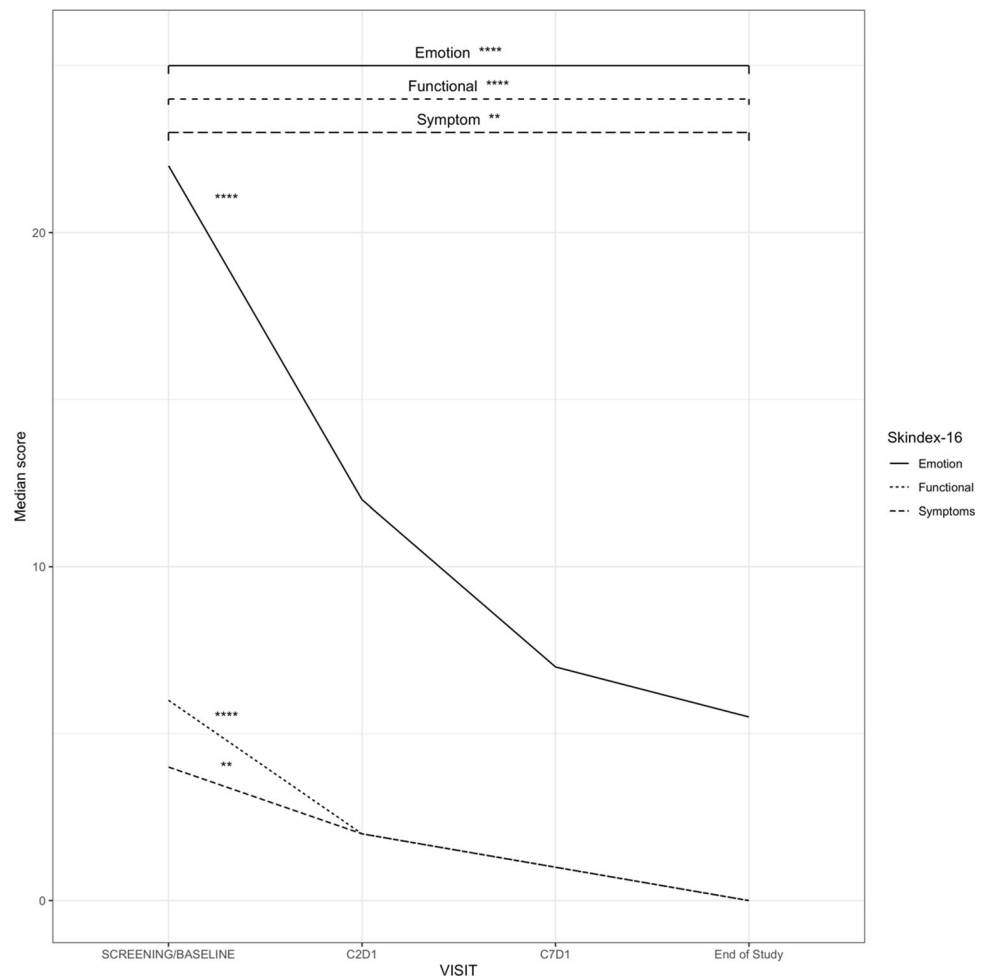


Table 3 Comparison of scores on the Skindex-16 HRQoL subscales between patients with POLA-BCC who completed the treatment and those who terminated their treatment due to adverse events.

	Completed treatment (N = 122)	Terminated treatment (N = 47)	p value
Treatment duration, days (mean (SD))	464 (424)	309 (230)	0.019
Baseline visit			
Symptom (mean (SD))	5.46 (6.13)	6.39 (5.87)	0.379
Emotion (mean (SD))	20.70 (13.45)	23.47 (12.24)	0.242
Functional (mean (SD))	9.60 (9.98)	8.49 (8.57)	0.504
C2D1			
Symptom (mean (SD))	3.95 (5.30)	3.95 (4.74)	0.999
Emotion (mean (SD))	14.68 (12.72)	13.28 (12.08)	0.546
Functional (mean (SD))	6.50 (8.50)	7.43 (9.31)	0.561
C7D1			
Symptom (mean (SD))	2.65 (3.64)	3.36 (5.56)	0.481
Emotion (mean (SD))	11.01 (11.45)	10.48 (12.86)	0.854
Functional (mean (SD))	4.92 (7.09)	4.96 (8.13)	0.985
End-of-study visit			
Symptom (mean (SD))	3.32 (5.05)	2.89 (4.74)	0.704
Emotion (mean (SD))	11.72 (13.85)	10.00 (10.40)	0.560
Functional (mean (SD))	5.21 (7.82)	4.48 (6.47)	0.667

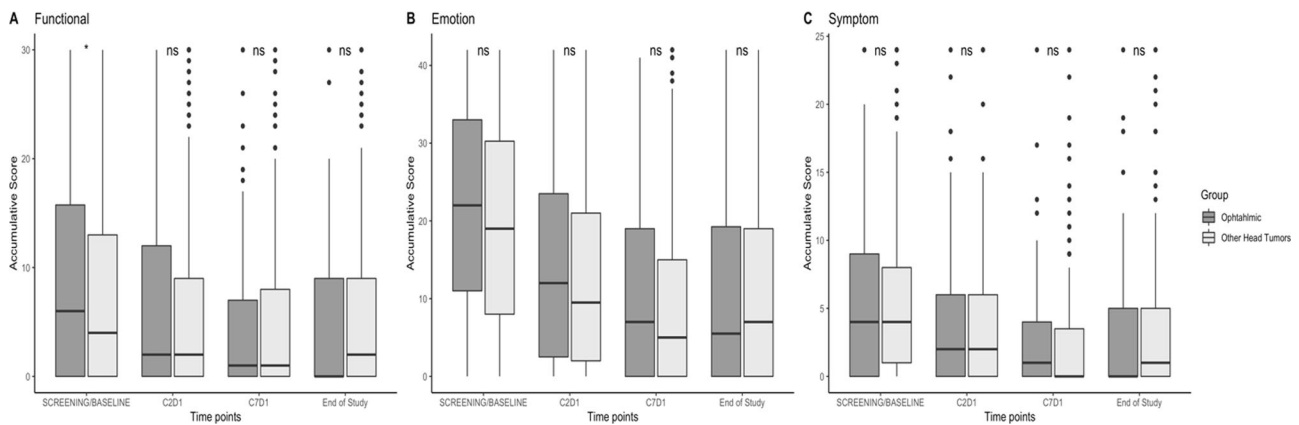


Fig. 2 Comparison of scores on the Skindex-16 HRQoL subscales (A - Functional, B - Emotion, C - Symptom) between patients with POLA-BCC and patients with other non-periocular head BCC.

The total score for the functional domain was significantly higher in the POLA-BCC group than the control group [6.00 (0.00, 17.00) vs 4.00 (0.00, 13.00), $p = 0.038$] at the baseline visit.

between-group differences in the other items addressing emotion: worry about the skin condition ($p = 0.198$), appearance of the skin ($p = 0.171$), frustration due to the skin condition ($p = 0.132$), embarrassment ($p = 0.083$), persistence or recurrence of condition ($p = 0.073$), and depression ($p = 0.306$).

Discussion

The primary objective of this secondary subgroup analysis of patients with POLA-BCC in the STEVIE study was to understand the impact of the disease and its treatment (vismodegib) on HRQoL over an extensive follow-up period. We found that POLA-BCC has an adverse impact on HRQoL and this was greatly ameliorated by vismodegib treatment (Fig. 1).

At baseline, patients with POLA-BCC exhibited a high emotional and symptomatic burden and impaired functioning. These findings are in line with previous studies on patients with all types of advanced BCC [17, 18]. Following vismodegib treatment, patients with POLA-BCC showed a significant improvement in all three major domains of the Skindex-16 relative to baseline, with emotional status improving by 75% and symptoms and functional status improving by 100%. In the original STEVIE study, clinically meaningful improvement was defined as a ≥ 10 -point decrease from baseline in the Skindex-16 score, and analysis of the cohort as whole (i.e., BCC at any anatomic location) yielded clinically meaningful vismodegib-associated improvement only in the emotions domain [12]. As the scores for symptoms and functioning were < 10 points at baseline, a reduction of more than 10 points using this tool was technically impossible. In contrast to our analysis, Hansson et al. [9] did not report the improvement in Skindex-16 scores as percentages of baseline. Thus, we cannot determine whether the significant

improvement in functioning and symptom scores in our study following vismodegib treatment are unique to the periocular subgroup or apply to the entire STEVIE cohort, especially as HRQoL scores responded positively to treatment in both of our groups, nearing normal values.

Our second objective was to compare the HRQoL of patients with POLA-BCC to patients with locally advanced BCC located elsewhere on the head (Fig. 2). The two groups shared many features in the emotions and symptoms domains, although there was an important difference in overall functioning score, which was higher at baseline in the POLA-BCC group, mainly in terms of ADL. This may be explained by the disabling nature of large periocular tumors which can affect functional vision via multiple mechanisms including direct compression, ptosis, ocular surface disturbances, and impaired motility. We expect to gain more insight into the vision-impairing effects of POLA-BCC and its response to treatment from the soon-to-be-published Vismodegib for Orbital and Periocular Basal Cell Carcinoma study [19], which offers a new metric for evaluation of the clinical response to treatment. In addition, studies have shown that disfiguring eye conditions cause high levels of psychological distress [14], which in this instance, may reduce functioning. The disruptive nature of an abnormal eye appearance in social interactions is also well documented. Studies of patients with strabismus reported adverse effects in many aspects of life, including finding a partner, job prospects, and interaction with peers [20]. However, the absence of a between-group difference in our study in baseline scores for emotions and symptoms suggests that ocular lesions are subjectively not more disfiguring than other head and face lesions.

Our results indicate that patients with POLA-BCC experience significant functional, symptomatic, and emotional distress as a consequence of their disease and these are improved with vismodegib treatment. While the main focus of treatment

is to control and perhaps cure POLA-BCC tumors, HRQoL should also be taken into account when choosing among potential treatment modalities. Funding for vismodegib was recently discontinued in several countries because the drug was not deemed cost-effective [21, 22]. Given the present findings, decision-makers might do well to consider excluding patients with POLA-BCC from this directive.

This study has some limitations. First, vismodegib has several very prevalent adverse effects including muscle spasms, alopecia, diarrhea, nausea, and fatigue [23], and we were unable to evaluate their influence on the Skindex-16 domain scores. Second, the Skindex-16 was not developed to evaluate specific ophthalmic manifestations such as decreased vision, dry eyes, and epiphora. We believe that a HRQoL instrument geared solely to patients with POLA-BCC is needed to better represent the functional and emotional toll of the disorder.

This is the first study to examine the HRQoL of patients with POLA-BCC. The main strengths of the study are the largest population of vismodegib-treated patients with POLA-BCC reported in the literature and the extensive follow-up period.

Summary

What was known before

- Vismodegib (Erivedge[®]) is emerging as the treatment of choice for locally advanced BCC.
- Severe disfigurement, blindness, and low vision, which may be a consequence of POLA-BCC, can lead to depression and anxiety.

What this study adds

- Patients with POLA-BCC experience significant functional, symptomatic, and emotional distress, improving with Vismodegib treatment.
- Decision-makers might do well to consider excluding patients with POLA-BCC from recent discontinuation of funding for Vismodegib in several countries.

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Author contributions AG and AT acquired the data and drafted the manuscript. MB-I and EB analyzed the data and aided in interpreting the results. GBS and IY designed the current study and revised the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethical approval This study was a secondary analysis of the STEVIE data and did not involve the recruitment of new participants. Therefore, institutional review board approval and patient consent were waived by our institutional protocol. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

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