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Research Article

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Vismodegib Treatment in Patients with Advanced Basal Cell Carcinoma: Long-Term Efficacy and Safety Data with Focus on Secondary Resistance and Underlying Resistance Mechanism

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Abstract

Background: *The smoothened inhibitor vismodegib is an effective targeted therapy for basal cell carcinoma (BCC) with a manageable and consistent safety profile. The occurrence of secondary resistance during treatment is a major problem and is associated with hedgehog pathway reactivation, predominantly through Smoothened (SMO) gene mutations.*

Objectives: *To analyse efficacy and safety data after long-term follow-up of patients treated with vismodegib for advanced BCC in the University Hospital of Leuven, focusing on underlying genetic mechanisms of primary and secondary resistance to vismodegib.*

Methods: *Twenty seven patients were retrospectively included in the study. We performed targeted sequencing of hedgehog pathway genes in 7 tumor samples from 4 patients with primary or secondary resistance to vismodegib.*

Results: *Mean duration of follow-up was 29.9 months (1-77.7 months). Mean treatment duration was 13.3 months (1-64.5 months). The response rate to vismodegib was 93% (25/27 patients), with a partial response in 18/27 patients and a complete response in 7/27 patients. One patient maintained a complete response up to >3 years after vismodegib discontinuation. Six out of 27 patients (24%) developed secondary resistance during treatment, in three of them we detected acquired pathogenic SMO mutations in resistant tumor tissue. One patient with Bazex–Dupré–Christol syndrome showed primary resistance to vismodegib. No unexpected safety signals were detected in our analysis, however progression of Multiple Sclerosis (MS) was observed in one patient.*

Conclusions: *We deliver new data about the response duration after vismodegib discontinuation and describe MS progression as a possible new adverse event to vismodegib. We describe for the first time vismodegib treatment and primary resistance to vismodegib in a patient with Bazex–Dupré–Christol syndrome. We highlight the problem of occurrence of secondary resistance in >20% of responders and confirm the previously reported resistance mechanism through acquired SMO mutations.*

Keywords: Basal Cell Carcinoma, Vismodegib, Vismodegib Resistance, Smoothened Mutations, Hedgehog Pathway

Introduction

Basal cell carcinoma (BCC) is the most common human cancer and is driven predominantly by overactivation of the hedgehog pathway. The majority of sporadic BCC harbour oncogenic alterations in genes of the hedgehog pathway resulting in constitutive pathway activation. Inactivating mutations in *PTCH1* are most commonly described (in about 70-80% of BCCs), followed by gain-of-function mutations in *SMO* (in about 6%-21% of BCCs), and to a lesser extent inactivating mutations in *SUFU.*[1] The oncogenesis of BCC has been elucidated by the study of genetic syndromes predisposing for BCC. Germline mutations in *PTCH1* cause Basal Cell Nevus Syndrome (BCNS) or Gorlin syndrome, an autosomal dominant disorder predisposing to the development of BCC at young age [1]. Patients with the rare X-linked dominantly inherited Bazex–Dupré–Christol syndrome (BDCS) develop BCC due to loss-of-function mutations in the *ACTRT1* gene, encoding for the actin-related protein T1 (ARP-T1) that has an inhibitory function on the downstream GLI transcription factors of the Hedgehog pathway [2].

The development of hedgehog pathway inhibitors provides a new treatment option for patients with locally advanced BCC (laBCC), metastatic BCC (mBCC) and BCNS patients. The smoothened inhibitor vismodegib is the first hedgehog pathway inhibitor that was approved by the US Food and Drug Administration in 2012 for the treatment of adults with laBCC or mBCC, followed by a second smoothened inhibitor sonidegib in 2015 [3-7].

Efficacy and safety data of vismodegib are based on two pivotal phase II clinical trials: the ERIVANCE trial (n=104 patients, primary endpoint efficacy, median follow-up duration 39.1 months in the final update of the ERIVANCE trial) and the STEVIE trial (n=1215 patients, primary endpoint safety, median follow-up duration 17.9 months) [3-5]. Vismodegib has shown to be an effective treatment for advanced BCC with a manageable and consistent safety profile. The ERIVANCE trial and STEVIE trial respectively report investigator assessed treatment responses of 60.3 and 68.5% in laBCC and 36.9 and 48.5% in mBCC. The current study presents long-term efficacy and safety data of vismodegib treatment for advanced BCC in a real-life clinical setting, with a follow-up duration up to 77.7 months.

Intolerance and the occurrence of secondary resistance to vismodegib are two major problems associated with vismodegib treatment. Most patients experience ≥1 adverse event. Although most adverse events are manageable and improve after ceasing treatment, the vast majority of patients has to discontinue treatment due to toxicity [5].

Up to 20% of responders develop secondary resistance to vismodegib during the first year of treatment, according to a retrospective case series of 28 patients [8]. In two papers published in 2015, Sharpe et al. and Atwood et al. performed genomic analysis of tumour tissue revealing a key role of hedgehog pathway reactivation in vismodegib resistance, predominantly through pathogenic mutations in *SMO* and to a lesser extent through copy number changes in *SUFU* and *GLI2* [9-11]. In the current study we highlight the problem of secondary resistance to vismodegib and investigate the underlying resistance mechanism in our patients by performing genetic analysis of resistant tumour tissue.

Methods

Retrospective chart review

We conducted a retrospective chart review of all adult patients who were treated with vismodegib for laBCC or mBCC at the department of Dermatology and Oncology in the University Hospital of Leuven between 03/2012 until 01/2019. Cut-off for inclusion of new patients and follow-up of included patients was 01/2019. The study protocol was approved by the local ethics committee.

Collected data include patient and tumour characteristics, duration of follow-up after treatment initiation (time from date of first treatment to date of last visit), total treatment duration (time from date of first treatment to date of last treatment, including treatment interruptions), number and duration of treatment interruptions. Efficacy variables include the physician-assessed treatment response defined as partial response (any clinical and/or radiological decrease in tumour size assessed by clinical examination or radiological assessment) or complete response (clinical and/or radiological disappearance of tumour; histological confirmation was done in cases where complete remission was doubted), time to response (TTR, time from date of first treatment to date of first documentation of response), total duration of response (DOR, time from date of first response to date of disease progression), primary resistance (lack of response to vismodegib from treatment start), and secondary resistance (clinical or radiological regrowth of BCC during vismodegib treatment after initial treatment response). Treatment interruptions are included in the total duration of response if the patient still responded to vismodegib after its reintroduction. Safety assessment included treatment emergent adverse events during treatment, including treatment interruptions.

DNA-extraction and sequencing of hedgehog pathway genes in tumour tissue

In all patients with primary or secondary resistance to vismodegib, we retrospectively collected preserved formalin-fixed paraffin-embedded (FFPE) or fresh frozen tumour tissue from the period before treatment as well as from the moment of occurrence of primary or secondary resistance to vismodegib. We collected 7 tumour samples from 4 patients with primary or secondary resistance. All tumour samples were subjected for next generation sequencing of hedgehog pathway genes *PTCH1*, *SMO*, *SUFU*, *GLI1* and *GLI2*. Analysis of copy number variation was not performed due to restrictions of our analysis pipeline.

Genomic DNA was extracted from fresh frozen or FFPE tumour tissue using the Maxwell 16 FFPE Tissue LEV DNA Purification Kit (Promega) on a Maxwell 16 instrument (Promega) or the Invisorb Spin Tissue Mini kit (Invitrogen). Prior to DNA extraction, manual macrodissection was performed to enrich for tumor content. Genomic DNA was fragmented enzymatically and libraries were prepared using the KAPA HyperPlus Library Preparation Kit (Kapa Biosystems, Wilmington, MA). Custom DNA probes targeting all exons of 97 cancer genes were used with the NimbleGen SeqCap EZ Library custom oligo system and were biotinylated to allow for sequence enrichment by capture using streptavidin-conjugated beads. Pooled libraries containing captured DNA fragments were subsequently sequenced on the Illumina sequencing instrument as 2 x 150-bp paired-end reads. The paired-end reads were mapped against the reference genome build 19 (GRCh37). Data analysis was performed using an in house developed bio-informatics pipeline based on fastq files, BWA for alignment, GATK for variant calling, and Annovar for variant annotation [12-14].

Results

Patient demographics and tumour characteristics

We included 27 patients (table 1). Seven patients were diagnosed with Basal Cell Nevus Syndrome (BCNS), of whom 5 patients were diagnosed by genetic analysis of a germline PTCH1 mutation and 2 patients by the diagnostic criteria for BCNS [15]. One patient was diagnosed with the X-linked dominantly inherited Bazex–Dupré–Christol syndrome (BDCS) based on the clinical and anamnestic features of follicular atrophoderma and milia in the face, multiple BCC at the age of 30 years, several spontaneous abortions and similar lesions in her mother's face [16].

Treatment efficacy

Mean duration of follow-up was 29.9 months (1-77.7 months). Mean treatment duration was 13.3 months (1-64.5 months). In 6/27 patients treatment was once or more frequently interrupted, in all of them because of intolerance to vismodegib. Duration of treatment interruptions varied from 0.6-21 months.

The response rate to vismodegib was 93% (25/27 patients), with a partial response in 18/27 patients (67%) and a complete response in 7/27 patients (26%). We note a short time to response with a mean TTR of 1.2 months (0.7-3 months). The mean total duration of response was 15.4 months (1.6-62.1 months). Of the 25 responders, 6 patients (24%) developed secondary resistance to vismodegib: 4 patients with sporadic BCC and 2 BCNS patients.

In the 19 responders who maintained treatment response until vismodegib discontinuation (excluding the six patients who developed secondary resistance), we evaluated the duration of treatment response after vismodegib discontinuation. In 12 evaluable patients we note a mean duration of response of 11.4 months after vismodegib discontinuation (1.1-40.1 months). Patient 8 maintained a complete response until data cut-off, up to 40.1 months after vismodegib discontinuation. Patients who achieved a complete response during treatment seemed to maintain the longest treatment responses after vismodegib discontinuation.

Two patients did not respond to vismodegib: patient 4 with BDCS and patient 6 with sporadic BCC. Patient 4 did not show any response to vismodegib after 3.7 months of treatment, considering this as primary resistance to vismodegib. In patient 6 the lack of response is probably due to the short treatment duration of 1.5 months (patient's choice). Excluding patient 6, would bring the response rate to 100% in patients with sporadic BCC and BCNS patients and would designate patient 4 with BDCS as the only patient showing primary resistance to vismodegib.

Table 1: Efficacy data: follow-up duration, total treatment duration, number of treatment interruptions, total duration of treatment interruptions, treatment response, time to response (TTR), secondary resistance (SR), total duration of response (DOR), duration of response after Vismodegib discontinuation. laBCC, locally advanced BCC, mBCC, metastatic BCC; BCNS, Basal Cell Nevus Syndrome; BDCS, Bazex- Dupré-Christol syndrome; DOR, duration of response; PR, partial response; CR, complete response; SR, secondary resistance

Patient	Age at treatment start	laBCC/ mBCC	Syn-dromic/ non-syn-dromic	Follow-up duration (months)	Total treatment duration (months)	Number of treatment interrup-tions	Total duration of treatment inter-ruptions (months)	Treatment response	TTR (months)	Secondary resistance (SR)	Total DOR (months)	DOR after Vismodeg-ib discon-tinuation (months)
1	71	laBCC	sporadic BCC	9	9	0	0	PR	2	SR	7	/
2	86	mBCC	BCNS	74.3	18.4	3	1.4	PR	1	SR	17.7	/
3	37	laBCC	BCNS	64.8	49.7	1	10.7	PR	2	SR	45.7	/
4	42	laBCC	BDCS	12.6	3.7	0	0	No re-sponse	/	-	0	/
5	63	mBCC	sporadic BCC	77.7	64.5	1	21	PR	1.2	SR	45	/
6	82	laBCC	sporadic BCC	2	1.5	0	0	No re-sponse	/	-	0	/
7	79	laBCC	sporadic BCC	9.6	4	0	0	CR	1	-	8.6	5.9 months
8	67	laBCC	sporadic BCC	63.1	23	0	0	CR	1	-	62.1	40.1 months
9	80	laBCC	sporadic BCC	19.2	4.5	0	0	PR	1.5	-	3	Not assess-able
10	67	laBCC	sporadic BCC	52.3	52.3	4	20.3	PR	1	-	51.3	Still in treatment
11	83	laBCC	sporadic BCC	49.1	2.3	0	0	PR	0.7	-	1.6	Not assess-able
12	66	laBCC	sporadic BCC	48.8	11	0	0	PR	0.9	SR	10.5	/
13	63	laBCC	sporadic BCC	39	27.3	1	18.4	PR	0.7	SR	6.3	/

14	75	laBCC	sporadic BCC	35	7	0	0	CR	1	-	34	28 months
15	52	laBCC	BCNS	47.5	30	2	23	PR	1	-	31.1	2.4 months
16	89	laBCC	sporadic BCC	5.7	4.6	0	0	PR	0.7	-	5.7	1.1 months
17	89	laBCC	sporadic BCC	1	1	0	0	PR	0.7	-	0.3	Not assessable
18	73	laBCC	BCNS	15.2	2	0	0	CR	0.7	-	9.3	8 months
19	61	laBCC	sporadic BCC	19.1	4	0	0	PR	1	-	3	Not assessable
20	82	laBCC	sporadic BCC	19.5	5	0	0	PR	1	-	13.6	8.6 months
21	53	laBCC	sporadic BCC	19	7.4	0	0	CR	3	-	16	11.5 months
22	76	laBCC	BCNS	21.2	3.7	0	0	PR	1	-	9	6.2 months
23	40	laBCC	BCNS	24.6	10	0	0	CR	0.7	-	15.7	7.4 months
24	49	laBCC	BCNS	24.4	3	0	0	PR	2	-	3.1	2.1 months
25	83	laBCC	sporadic BCC	19.5	4	0	0	PR	2	-	2	Not assessable
26	74	laBCC	sporadic BCC	14.3	2.7	0	0	PR	1	-	2.2	Not assessable
27	45	laBCC	sporadic BCC	19.3	3	0	0	CR	1	-	18.2	15.6 months
Mean	68			29.9	13.3	0.4	3.5		1.2		15.4	11.4

Treatment safety

All patients experienced ≥1 adverse event. Most adverse events were manageable, but intolerance was the main reason for treatment interruption and treatment discontinuation. The most frequent adverse events in order of frequency were: myalgia/artralgia in 23/27 patients (85%), dysgeusia in 21/27 patients (78%), fatigue in 13/27 of patients (48%), loss of appetite in 11/27 patients (41%), diarrhea in 10/27 patients (37%), weight loss in 10/27 patients (37%), hair loss in 10/27 patients (37%), nausea in 8/27 patients (30%). All of these adverse events are common and well-known adverse events during vismodegib treatment.(4,5) Less frequent adverse events were headache in 3/27 patients (11%) and dizziness in 2/27 patients (7,4%). Remarkable one patient with Multiple Sclerosis (MS) showed neurological deterioration as a possible, yet not previously described, adverse event to vismodegib. He presented with paraesthesias and walking difficulties during vismodegib treatment, which ameliorated after vismodegib discontinuation. The causality between his neurological symptoms and vismodegib treatment remains uncertain, although it is conceivable that the general deterioration of the patients performance status was at least partially linked to neurological deterioration.

One patient deceased during follow-up after vismodegib treatment at the age of 75 due to progressive lymph node and liver metastasized BCC (patient 2).

Genetic analysis of hedgehog pathway genes in vismodegib-resistant BCC

From patient 1, 2 and 3 with secondary resistance to vismodegib, we disposed of preserved tumour tissue from the period before treatment and from the moment of secondary resistance. From patient 4 with primary resistance to vismodegib, we only disposed of preserved tumour tissue from the period after treatment. Taken together we subjected 7 tumour samples to targeted sequencing of the hedgehog pathway genes *PTCH1*, *SMO*, *SUFU*, *GLI1* and *GLI2*. The results are shown in table 2. We found mutations in hedgehog pathway genes *PTCH1* and *SMO*. The pre-treatment tumour sample of patient 2 was not interpretable due to insufficient quality and quantity of the tumour DNA and quality of the sequence data (coverage of 5x).

*PTCH*1 VARIANTS

In patient 1 with sporadic BCC we found a *PTCH1* null variant c.864_867delinsCTA (p.(His289*)) in both pre-and post-tumour tissue, very likely to be the oncogenic driver of the tumour due to loss-of-function of *PTCH1*. Both BCNS patients 2 and 3 harbour a *PTCH1* germline variant causing BCNS syndrome: respectively c.2961del (p.(Phe987Leufs*8)) and c.1599dup (p.(Glu534*)). These germline *PCTH1* mutations are present in all of their analysed tumour samples and are confirmed in a patient's family member (patient 2) and a patient's blood sample (patient 3). We note that the pre-treatment tumour sample of patient 2 is not interpretable. In the tumour tissue of patient 2 at moment of secondary resistance we found a second *PTCH1* variant c.3715C>T (p.(Arg1239Trp)), of which the biological significance is currently unknown (Variant of Unknown Significance).

SMO VARIANTS

Genetic analysis of tumor tissue at moment of secondary resistance in patient 1, 2 and 3 reveals the presence of pathogenic *SMO* variants c.1234C>T (p.(Leu412Phe)) and c.1376C>T (p.(Ala459Val)), which are not present in the corresponding pre-treatment tumor samples. These *SMO* mutations have been reported to cause vismodegib resistance, confirmed by cell-based functional studies and/or computer modeling predicting altered binding affinity [9-11].

In patient 4 with BDCS and primary resistance to vismodegib, we did not find any genetic variation in the investigated hedgehog pathway genes in tumor tissue at moment of 3.7 months of treatment. We

note that analysis of copy number variations was not performed in this study.

Table 2: Results of next generation sequencing of Hedgehog genes PTCH1 (NM_000264.4), SMO (NM_005631.4), SUFU (NM_016169.3), GLI1 (NM_005269.2) and GLI2 (NM_005270.4) in tumor tissue before treatment and tumor tissue from the moment of primary or secondary resistance. BCNS, Basal Cell Nevus Syndrome; BDCS, Bazex- Dupré-Christol syndrome; PTCH1, Patched 1; SUFU, Supressor of Fused; SMO, Smoothened; GLI, glioma-associated oncogene transcription factors; n/a, non applicable

Patient/ Syndrome	Gene	Germline gene mutation	Gene mutations in tumor tissue before treatment	Gene mutations in tumor tissue from the moment of primary or secondary resistance
Patient 1 Sporadic BCC	PTCH1	n/a	c.864_867delinsCTA (p.(His289*)) (exon 6)	c.864_867delinsCTA (p.(His289*)) (exon 6)
	SMO	n/a	-	c.1234C>T (p.(Leu412Phe)) (exon 6)
	SUFU	n/a	-	-
	GLI1	n/a	-	-
	GLI2	n/a	-	-
Patient 2 BCNS	PTCH1	c.2961del (p.(Phe987Leufs*8)) (exon 18)**	Not interpretable	c.2961del (p.(Phe987Leufs*8)) (exon 18) c.3715C>T (p.(Arg1239Trp)) (exon 22)
	SMO		Not interpretable	c.1376C>T (p.(Ala459Val)) (exon 8)
	SUFU		Not interpretable	-
	GLI1		Not interpretable	-
	GLI2		Not interpretable	-
Patient 3 BCNS	PTCH1	c.1599dup (p.(Glu534*)) (exon 11)***	c.1599dup (p.(Glu534*)) (exon 11)	c.1599dup (p.(Glu534*)) (exon 11)
	SMO		-	c.1376C>T (p.(Ala459Val)) (exon 8)
	SUFU		-	-
	GLI1		-	-
	GLI2		-	-
Patient 4 BDCS	PTCH1	n/a	Not analysed	-
	SMO	n/a	Not analysed	-
	SUFU	n/a	Not analysed	-
	GLI1	n/a	Not analysed	-
	GLI2	n/a	Not analysed	-

** germline PTCH1 mutation confirmed in patient's daughter with BCNS
*** germline PTCH1 mutation confirmed in a patient's blood sample

Discussion

This study presents long-term efficacy and safety data of vismodegib treatment for advanced BCC in a real-life clinical setting, with a follow-up duration up to 77.7 months.

We present new data about the durability of response after vismodegib discontinuation. A previous patient survey of 13 patients following the primary analysis of the ERIVANCE trial in 2015 suggested that patients may maintain treatment response for >1 year after vismodegib discontinuation [17]. We describe a sustained complete treatment response up to >3 years after vismodegib discontinuation. Patients who achieve a complete response during vismodegib treatment seem to maintain the longest treatment responses after vismodegib discontinuation.

In the current study we focuss on the problem of secondary resistance to vismodegib. A previous retrospective case series of 28 patients reported occurrence of secondary resistance in up to 20% of patients [8]. We provide additional data with a similar rate of secondary resistance in 24% of our patients. We additionally investigated the underlying resistance mechanism by performing genetic analysis of vismodegib resistant tumor tissue, confirming the previously reported resistance mechanism through acquired pathogenic SMO mutations [9-11].

Our cohort also included a patient with Bazex–Dupré–Christol syndrome (BDCS), showing primary resistance to vismodegib. To our knowledge no data are available about vismodegib treatment in patients with BDCS. BDCS is a rare X-linked dominant genodermatosis characterized by a triad of hypotrichosis, follicular atrophoderma and multiple basal cell carcinoma [16]. The causative genetic defect on the X-chromosome remained unknown for many years, but a recent study in 2017 identified germline loss-of-function mutations in the *ACTRT1* gene [2]. The *ACTRT1* gene encodes for the ARP-T1 protein, which has an inhibitory function on the downstream GLI transcription factors of the hedghog pathway. With this knowledge it is conceivable that BDCS patients do not respond to vismodegib, since vismodegib targets the SMO protein more upstream in the hedgehog pathway. We report the first clinical case of a BDCS patient with primary resistance to vismodegib.

No unexpected safety signals were detected in our analysis. However in one patient with Multiple Sclerosis we noted neurological deterioration as a possible adverse event to vismodegib. As far as we are concerned, no previous cases of vismodegib-induced neurological symptoms in MS patients have been reported. Hedgehog signalling has been shown to play a major role in the development, maintenance and repair of the central nervous system. Hedgehog signalling is altered in several neurological disorders including the demyelinating disease MS. The hedgehog pathway is vital for the development of oligodendrocytes, the glial cells responsible for axon (re)myelination that are affected in MS patients. Moreover, upregulation of the hedgehog pathway by targeting SMO is suggested as a promising target for treatment of demyelinating disorders including MS. It is therefore tempting to speculate that MS progression by downregulation of the hedgehog pathway under vismodegib treatment occurs. However, more data from patients registries should be collected in order to confirm this observation.

Compared to previous studies, we describe a high response rate to vismodegib with a short time to response. This is probably due to the fact that our data are non-standardized in contrast to the ERIVANCE and STEVIE trial with standardized data conform the RECIST criteria (Response Evaluation Criteria in Solid Tumors), wherein response is defined as at least a decrease of 30% in the sum of diameters according to the baseline tumor. The retrospective nature of the study as well as the non-standardized physician-assessed data collection and the small study population are clear limitations of this study.

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