Secondary resistance to Vismodegib through acquired pathogenic SMO mutations: a case series.

L. Van Eecke[1], S. Vander Borght[2], I. Vanden Bempt[3], S. Lehnert[4], E. Hauben[2], H. Brems[3], E. Legius[3], J. Van den Oord[2], P. Wolter[5], O. Bechter[6], M. Garmyn[1]

1 Dpt. Dermatology, UZ Leuven, Leuven, Belgium; 2 Dpt. Pathology, UZ Leuven, Leuven, Belgium; 3 Centre for Human Genetics, UZ Leuven, Leuven, Belgium; 4 Dpt. Genomics Core, UZ Leuven, Leuven, Belgium; 5 Dpt. Oncology, Hospital St. Nikolaus, Eupen, Belgium; 6 Dpt. Oncology, UZ Leuven, Leuven, Belgium

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. [1-2]

Objectives and methods

We performed targeted sequencing of hedgehog pathway genes in 7 tumour samples from 4 patients with primary or secondary resistance to vismodegib, to investigate the underlying genetic mechanisms of primary and secondary resistance to vismodegib. All tumour samples were subjected for next generation sequencing of hedgehog pathway genes *PTCH1*, *SMO*, *SUFU*, *GLI1* and *GLI2*.

Results

In three patients (patient 1, 2 and 3) with secondary resistance to Vismodegib, we detected acquired pathogenic *SMO* variants in resistant tumour tissue, which were not present in the corresponding pre-treatment tumour samples. In patient 4 with primary resistance to vismodegib, we did not find any genetic variation in resistant tumour tissue after 3.7 months of treatment.

Conclusion

We confirm the previously reported mechanism of secondary resistance of basal cell carcinoma to Vismodegib through acquired pathogenic *SMO* mutations. We demonstrate drug-induced selection of *SMO* mutations by comparing pre-treatment and post-treatment tumour tissue. Acquiring more knowledge about the resistance mechanisms of BCC to vismodegib is useful to guide future treatment strategies. The development of a next generation of hedgehog pathway inhibitors targeting GLI-activity downstream of SMO is urging to overcome the problem of SMO-inhibitor resistance. In addition, genetic analysis of Hedgehog genes in (resistant) tumour tissue of individual patients could guide further treatment choices as a form of “personalized medicine”.

Hedgehog pathway

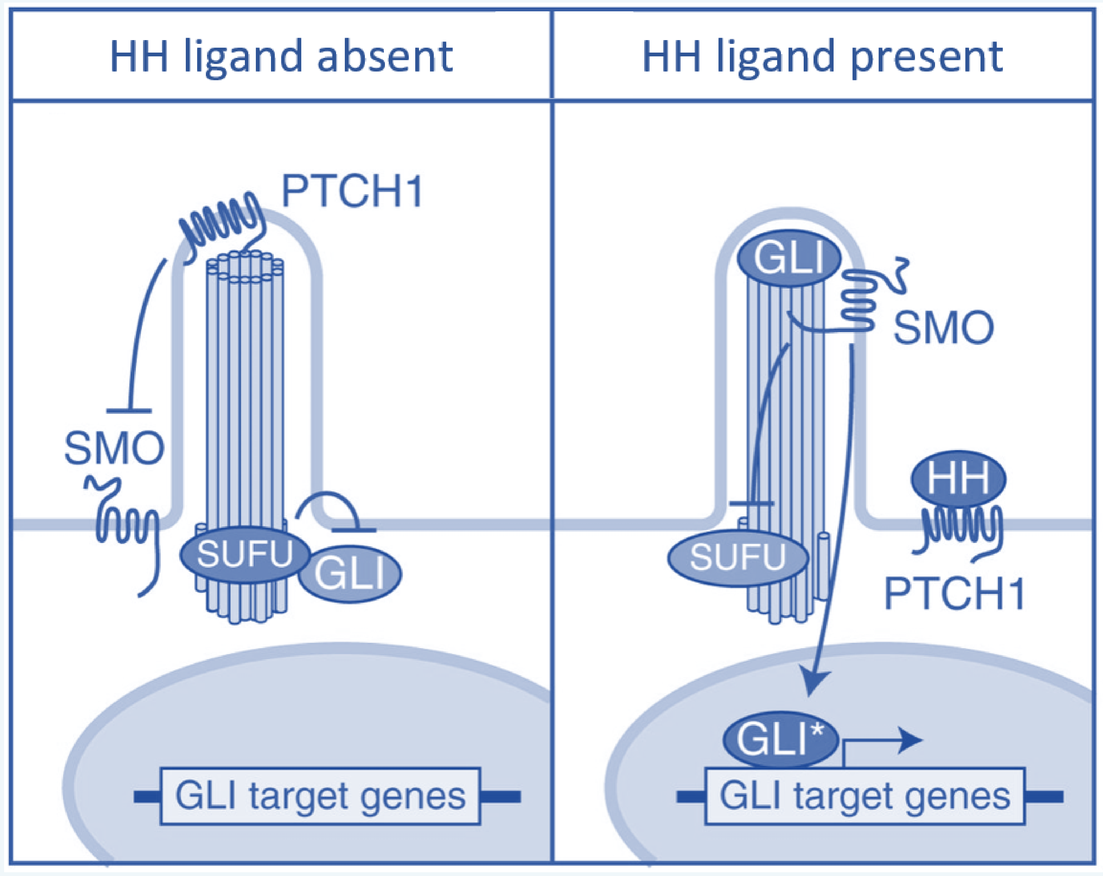

Figure 1. Schematic overview of the hedgehog pathway and its containing proteins: PTCH1 and SUFU have respectively an inhibitory function and SMO an activating function on the GLI-transcription factors, which induce hedgehog pathway activation.[1] PTCH1, Patched 1; SUFU, Supressor of Fused; SMO, Smoothened; GLI, glioma-associated oncogene transcription factors.

References

1. Sharpe HJ, Pau G, Yauch RL et al. Genomic Analysis of Smoothened Inhibitor Resistance in Basal Cell Carcinoma. Cancer Cell 2015;27(3):327–41.
2. Atwood SX, Sarin KY, Whitson RJ et al. Smoothened variants explain the majority of drug resistance in basal cell carcinoma. Cancer Cell 2015;27(3):342–353.

Results of next generation sequencing of Hedgehog genes *PTCH1*, *SMO*, *SUFU*, *GLI1* and *GLI2*

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

Table 1. 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.

liesbeth.vaneecke@uzleuven.be