Treatment of VHL Patients with Sunitinib: Clinical Outcomes And Translational Studies

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Introduction

von Hippel Lindau (VHL) disease is an autosomal dominant disorder that affects approximately one in 35 000 individuals. Patients develop vascular lesions in the cerebellum, brainstem, spinal cord, retina, kidney, pancreas and adrenal gland. These lesions arise due to the failure of mutated VHL to regulate hypoxia inducible factors (HIF), which results in the unbridled transcription of proangiogenic factors, including vascular endothelial growth factor (VEGF).[1]

To date, four anti-VEGF therapies have been approved for use in renal cell carcinoma,[2,3,4,5] and several others are in clinical trials. We hypothesized that treatment of VHL related lesions with sunitinib, a relatively potent small molecule inhibitor of VEGF and platelet derived growth factor would be safe, and would result in shrinkage of VHL related lesions.

To better understand the differences between various VHL related lesions, we analyzed the activation state of various proangiogenic endothelial receptors in RCC and central nervous system hemangioblastomas (Hbs).

Objectives

Primary: Assess safety of sunitinib in patients with VHL.
Secondary: Assess sunitinib efficacy in patients with VHL.

Methods

Study Design: Prospective open label single arm study.
Inclusion:
1.Patients with genetically confirmed VHL
2.Presence of measurable malignant lesions in kidney (1-3cm in size) or pancreas (1-3cm in size); Hb $\geq$ 0.5cm in cerebellum, brainstem, or spinal cord; retinal hemangiomas; other VHL related lesions.
3.Not in immediate need for surgical intervention
Exclusion:
1.Metastatic disease
2.Pheochromocytoma

Clinical Evaluation: Baseline and follow-up evaluations of target lesions were performed by using computed tomography (CT) scanning or magnetic resonance imaging (MRI. Reimaging was performed after the second and fourth cycles. Direct ophthalmoscopy, using fluorescein angiography with photographs, color testing, and visual field testing, was used to follow retinal lesions.

Methods cont.

We used RECIST, modified to uncouple organ systems: each organ system was evaluated separately. Sunitinib Dosage: Patients were given oral sunitinib at a dosage of 50 mg daily for 28 days, followed by a 14-day break, for up to four cycles. Up to two dose reductions were permitted in 12.5mg increments.

Archived Tissue Analysis: After obtaining IRB approval, we retrieved 20 sequential formalin-fixed and paraffin-embedded specimens each of VHL-related HBs and sporadic RCCs at random from The University of Texas M. D. Anderson Cancer Center tissue bank. The specimens were analyzed at ApoCell, Inc. (Houston, TX), by using a laser-scanning cytometer (CompuCyte Corporation, Cambridge, MA). Tissues were stained with CD31 (M0823, DakoCytomation), phosphorylated VEGFR2 (pVEGFR2; PC460, Calbiochem), VEGFR2 (SC-19530, Santa Cruz), FGFR3 (4574, Cell Signaling), Tie2 (334208, Biolegend), pPDGFR-beta (SC-12909-R, Santa Cruz), PDGFR (SC-339-G, Santa Cruz), and pFRS2 (3864, Cell Signaling) antibodies, followed by species-specific secondary antibodies conjugated to fluorescent dyes (Cy5/FITC/PE; Jackson ImmunoResearch Laboratories).

Statistical Analysis: This study was designed to include a maximum of 28 patients, but it would be stopped early if the data from a continuous evaluation of toxicity suggested that P (treatment terminating toxicity > 0.3 | data) > 90%.

Statistical Analysis

Enrolling 14 patients would yield 83% power to detect the difference between then null hypothesis proportion of 5% response rate (PR + CR) and the alternative proportion, 30%, using an exact binomial test with a two-sided significance level of 10%, while enrolling 28 patients would yield 95% power to detect the difference between the null hypothesis proportion of 5% response rate (PR + CR) and the alternative proportion, 30%, using an exact binomial test with a two-sided significance level of 5%.

Table 1. Response to Therapy

		Best Response		
Lesion Type	No. of Lesions	Partial Response	Stable Disease	Progressive Disease
Hemangioblastoma	21	0	19 (91)	2 (9)
Renal cell carcinoma	18	6 (33)	10 (67)	2 (10)
Renal cyst	9	0	9 (100)	0
Retinal angioma	7	0	7 (100)	0
Pancreatic NET	5	0	5 (100)	0
Pancreatic cyst	3	0	3 (100)	0

Results

15 patients were enrolled. All 15 patients received at least two cycles of therapy; 9 received all four.

Table 2: Analysis of RCC and Hb Endothelial Receptor/Activation

Receptor*	Tissue	log(Hemangioblastoma) Mean (SD)		log(RCC) Mean (SD)		P Value (t Test)	P Value (Wilcoxon's Rank -Sum Test)
pVEGFR2	Endothelium	11.268	0.498	11.752	0.378	0.001	0.003
VEGFR total	Endothelium	12.977	0.478	13.081	0.859	0.639	0.192
pPDGFR	Endothelium	10.952	0.654	10.805	0.839	0.539	0.82
PDGFR total	Endothelium	13.078	0.659	12.842	0.851	0.333	0.947
VEGFR ratio	Endothelium	0.206	0.122	0.372	0.431	0.105	0.043
PDGFR ratio	Endothelium	0.145	0.067	0.157	0.077	0.608	0.602
Tie2	Endothelium	12.654	0.455	12.63	0.817	0.909	0.883
Tie2	Whole Tumor	11.598	0.321	11.614	0.303	0.866	0.947
FGFR3	Endothelium	12.265	0.448	12.29	0.961	0.914	0.495
FGFR3	Whole Tumor	11.439	0.224	11.338	0.106	0.0075	0.174
pFRS2	Endothelium	12.495	0.492	11.91	0.989	0.023	0.059
pFRS2	Whole Tumor	11.452	0.258	11.258	0.089	0.003	0.003

Results continued

The major reasons for treatment discontinuation included patient choice (in 3), clinical progression (in 2), and therapy-related toxicity (neutropenia in 1). The patient choice category included patients who experienced toxic effects that did not reach grade 3 or 4 severity but who decided to discontinue treatment because of drug-related quality-of-life issues. Adverse side effects included fatigue, diarrhea, mucositis, anemia, nausea, and hypertension. Grade 3 toxicity included fatigue in five patients (33%), hand-foot syndrome in two patients (13%), nausea in two (13%), hypertension in one (7%), and neutropenia in four (26%). No grade IV or V toxicities were encountered. The daily dosage of sunitinib was reduced in 10 patients: to 37.5 mg in six and to 25 mg in four.

Response to therapy is summarized in Table 1. There was a significantly greater response to sunitinib in RCC lesions compared to Hbs(p=0.022). Receptor levels in RCC and Hb endothelium are summarized in Table 2. Phospho VEGFR2 and VEGFR ratios were higher in RCC, whereas pFRS2 was trending higher in Hb endothelium and was clearly higher in total Hb tissue when compared to RCC.

Conclusions

Treatment of VHL patients with sunitinib therapy was safe and relatively tolerable. Consistent response was seen in RCC lesions, but not in Hbs. These differences may be explained by differential expression and activation of specific endothelial receptors, and raises the hypothesis that treatment of Hbs with anti-FGF targeted therapy may be efficacious.

References

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