

CLINICAL CASE REPORT



A retrospective case study of sunitinib treatment in three patients with Von Hippel-Lindau disease

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ABSTRACT

Von Hippel-Lindau (VHL) disease is characterized by malignant and benign tumors in multiple organs. Sunitinib, a tyrosine kinase inhibitor, has been clinically available for treating sporadic patients with recurrent or unresectable and metastatic clear renal cell carcinomas (cRCCs) and metastatic lesions of the lung, but its effect on VHL disease-associated tumors remains poorly understood. This retrospective case series examined the effect of sunitinib on RCC, hemangioblastomas, pheochromocytomas, and pancreatic neuroendocrine tumors in patients with confirmed VHL. Of note, three patients with VHL disease who were treated with sunitinib were identified from a review of their medical records. The efficacy of sunitinib was evaluated by comparing computed tomography (CT) or magnetic resonance imaging (MRI) scans conducted before and after treatment. Adverse side effects associated with sunitinib were assessed and recorded. All three patients with VHL disease exhibited clinical improvement after treatment with sunitinib. Patient 1 exhibited a decrease in the size of both their pheochromocytoma and RCC after 19 months of sunitinib treatment. RCCs in Patients 2 and 3 exhibited stable response to sunitinib for approximately 1 and 6 years, respectively. All the patients reported tolerable side effects. Therefore sunitinib treatment was associated with either partial response or stable control of VHL-related RCCs, pheochromocytomas and pancreatic neuroendocrine tumor (NET) with acceptable side effects. Further evaluation of sunitinib in patients with VHL disease in larger prospective studies is warranted.

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Introduction

Von Hippel-Lindau (VHL) disease, a rare autosomal dominant tumor syndrome caused by a germline mutation in the *VHL* gene, is characterized by the occurrence of multiple malignant and benign tumors in various organs, including retinal hemangiomas, hemangioblastomas of the central nervous system, pancreatic neuroendocrine tumors or cystadenomas, pheochromocytomas, and clear cell renal cell carcinomas (cRCCs).^{1,2} The wild-type VHL protein exerts tumor-suppressive functions primarily by binding directly with hypoxia-inducible factors (HIF-1 α and HIF-2 α), which promotes their proteasomal degradation via ubiquitylation. The mutant VHL protein lacks this ubiquitin ligase activity, however, which ultimately results in increased levels of HIFs and the activation of their downstream pathways, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF)- α related pathways.³ Loss-of-function alterations in VHL therefore contribute to the carcinogenesis observed in both VHL-related and most sporadic cases of cRCC.

Hypoxia-induced activation of the VEGF pathway has been implicated in the pathogenesis of RCC. Molecular therapies that target components of the VEGF pathway have been

developed to treat sporadic RCC. Sunitinib, an oral multi-kinase inhibitor that targets VEGF, PDGF, KIT, and FLT3 receptors,⁴ is clinically available for treating sporadic patients with recurrent or unresectable and metastatic cRCCs and metastatic lesions of the lung.⁵ In addition, sunitinib also has been used for the treatment of pancreatic neuroendocrine tumors, but has been shown to be less effective in treating lesions of the kidney.⁶ To date, however, only a few large prospective studies have been conducted to test the efficacy of sunitinib in patients with VHL disease. It remains to be clarified, therefore, whether treatment with sunitinib is similarly effective for patients with VHL disease-associated tumors.

Results

Patients

Patient 1: A female was diagnosed with bilateral pheochromocytomas at age 29 when she presented with severe hypertension and two large masses (greater than 6 cm) in her bilateral adrenal glands. She underwent bilateral adrenal resections within one year of her diagnosis. At 38 years old, she underwent a resection for a mass found on her pancreas; this procedure was complicated by pancreatic leakage that persisted for more than

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6 months to heal. Pathological analysis of the mass revealed a pancreatic neuroendocrine tumor. At 40 years old, a blood DNA analysis was given and identified a well-known pathogenic *VHL* mutation c.239G>T; p.(Ser80Ile), which is associated with a severe phenotype. At 42 years old, a follow-up CT scan revealed two heterogeneous contrast-enhanced masses, one on the right kidney (2.5 × 2.1 cm; **Figure 1A**) and one on the left adrenal gland (6.1 × 3.9 cm; **Figure 1C**). Given her

surgical history, including last surgical complications, and multiple recurrent lesions, the patient was unsuitable for further surgery and started on oral administration of sunitinib. After 11 months, she experienced severe dizziness, headache, and emesis, and a head MRI scan revealed a 1.0 × 1.4 cm lesion in her right cerebellum (**Figure 1E**). The patient underwent a mass resection in her right cerebellum after 2 weeks sunitinib use was terminated. Subsequent pathological evaluation

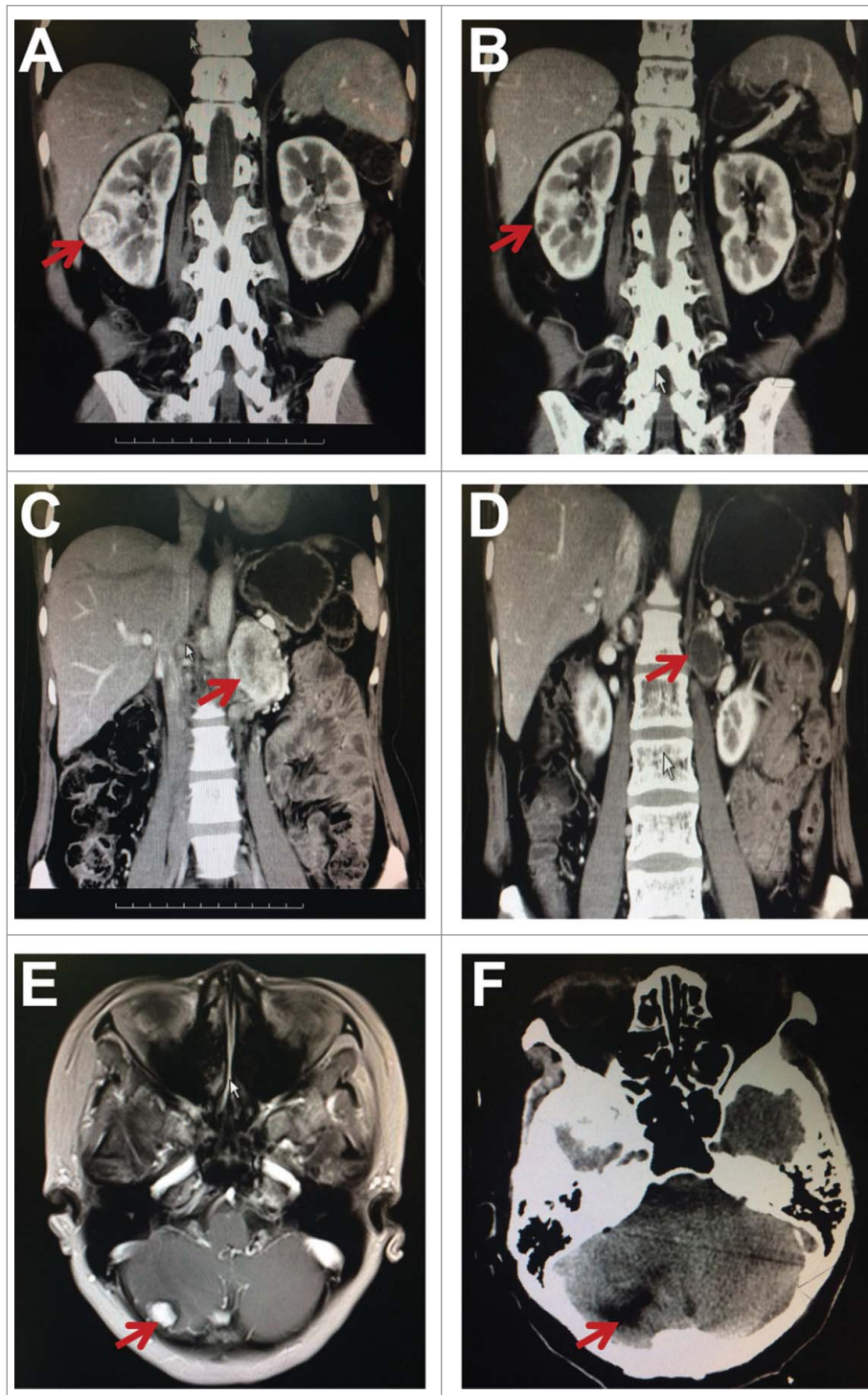


Figure 1. Computed tomography (CT) and magnetic resonance imaging (MRI) scans from Patient 1. The CT scans show the right renal cell carcinoma (RCC) and left pheochromocytoma before (A, C) and after (B, D) sunitinib treatment. The MRI scans show the hemangioblastoma in the right cerebellum before sunitinib treatment (E) and the CT scan shows the site of the lesion after the operation (F). Red arrows indicate the masses.

confirmed a hemangioblastoma. Sunitinib was prescribed again after one month after the operation. Follow-up duration for sunitinib administration lasted 2.5 years.

The patient has a notable family history. Her eldest brother had multiple RCCs in both kidneys, bilateral cerebellar hemangioblastomas, and pheochromocytoma in his left adrenal gland (see Patient 2). Her daughter also underwent cortex-sparing adrenalectomies for bilateral pheochromocytomas as well as hemangioblastoma resection in her left cerebellum at age of 19 years.

Patient 2: The brother of Patient 1 was referred to our hospital at 38 years old for bilateral hemangioblastomas in the cerebellum. In both 2001 and 2002, he underwent mass resections for these tumors. In 2009, an MRI scan revealed a 2.2×2.1 cm mass in his cerebellum, for which he underwent γ -knife treatment. In December 2013, a CT scan of his abdomen revealed uncountable masses in the whole left kidney and 1 mass in the left adrenal gland as well as 4 lesions in the right kidneys (Figure 2A-D). Pancreas appeared normal. The patient underwent the left nephrectomy and resection of the left adrenal mass. The pathological examinations confirmed cRCC in his left kidney and pheochromocytomas in his left adrenal gland. Sanger sequencing of the *VHL* gene revealed the same *VHL* mutation (c. 239G>T; p. Ser80Ile) that was identified in Patient 1. The masses in his right kidney were left and the patient started on oral administration of sunitinib in January 2017 and duration of sunitinib administration had lasted for almost one year.

Patient 3: In August 2011, a 50-year-old female was admitted to our hospital where a MRI scan revealed at least 3 lesions on her left kidney (Figure 3A and B) and 3 lesions in her pancreas (Figure 3C), which were most likely to be pancreatic NETs according to the characteristics on MRI scans. The size of the largest tumor on her kidney is about 3.1×2.4 cm. MRI scan on brain was negative and the abdominal CT scan discovered a mass with contrast enhancement on her back

(Figure 3D) Five years ago before this admission, the patient had undergone a radical nephrectomy for the tumors on the right kidney. Given that the patient had solitary kidney and multiple tumors in her left kidney and pancreas, she was started on sunitinib to control the tumor. Since then, sunitinib had been administrated for total of 6 years. In 2012, A blood DNA sequencing analysis revealed a pathogenic *VHL* mutation c. 232A>T; p. Asn78Tyr in this patient. The same point mutation of *VHL* was identified in three family members including one sister, one brother and one nephew. Her sister was found with pancreatic NET and died of the hemorrhagic stroke at age of 40 years, and her brother and nephew refused for further examinations for *VHL*-related lesions. Her mother died of stroke at early of 50 years.

Clinical outcomes and therapeutic response

The clinical characteristics of the three patients are reported in Table 1. During the follow-up period, CT or MRI scans were conducted every 3–4 months to evaluate the responses of the tumors to sunitinib treatment. All three patients showed clinical improvement after treatment with sunitinib. In Patient 1, the representative CT scan after sunitinib treatment was performed in October 2016, which was 19 months after the start of sunitinib treatment. This scan revealed that the size of the RCC (Figure 1B) had decreased from 2.5×2.1 cm before sunitinib treatment to 1.1×0.9 cm after treatment. Similarly, the size of the left pheochromocytoma (Figure 1D) had decreased from 6.1×3.9 cm before sunitinib treatment to 3.3×2.4 cm after treatment (Table 2). More importantly, a reduction of iodine uptake was found in the tumors compared with baseline scans, suggesting necrosis of the tumor cells occurred after sunitinib treatment. Moreover, the size of the hemangioblastoma in her right cerebellum also seemed to decrease from 1.0×1.4 cm before sunitinib treatment to 1×1 cm during surgery, which was conducted after 11 months of sunitinib treatment. A post-

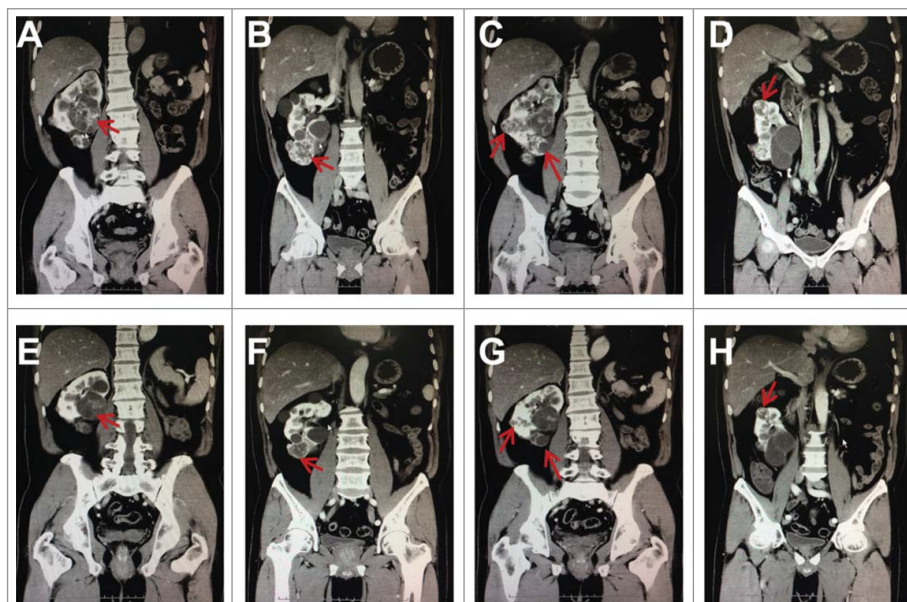


Figure 2. Computed tomography (CT) scans from Patient 2. The CT scans show multiple right renal cell carcinomas (RCCs) before and after sunitinib treatment, including the masses around the renal hilum (A and E), lower ventral (B and F), dorsal, lower dorsal (C and G), superior pole (D and H). Red arrows indicate the masses.

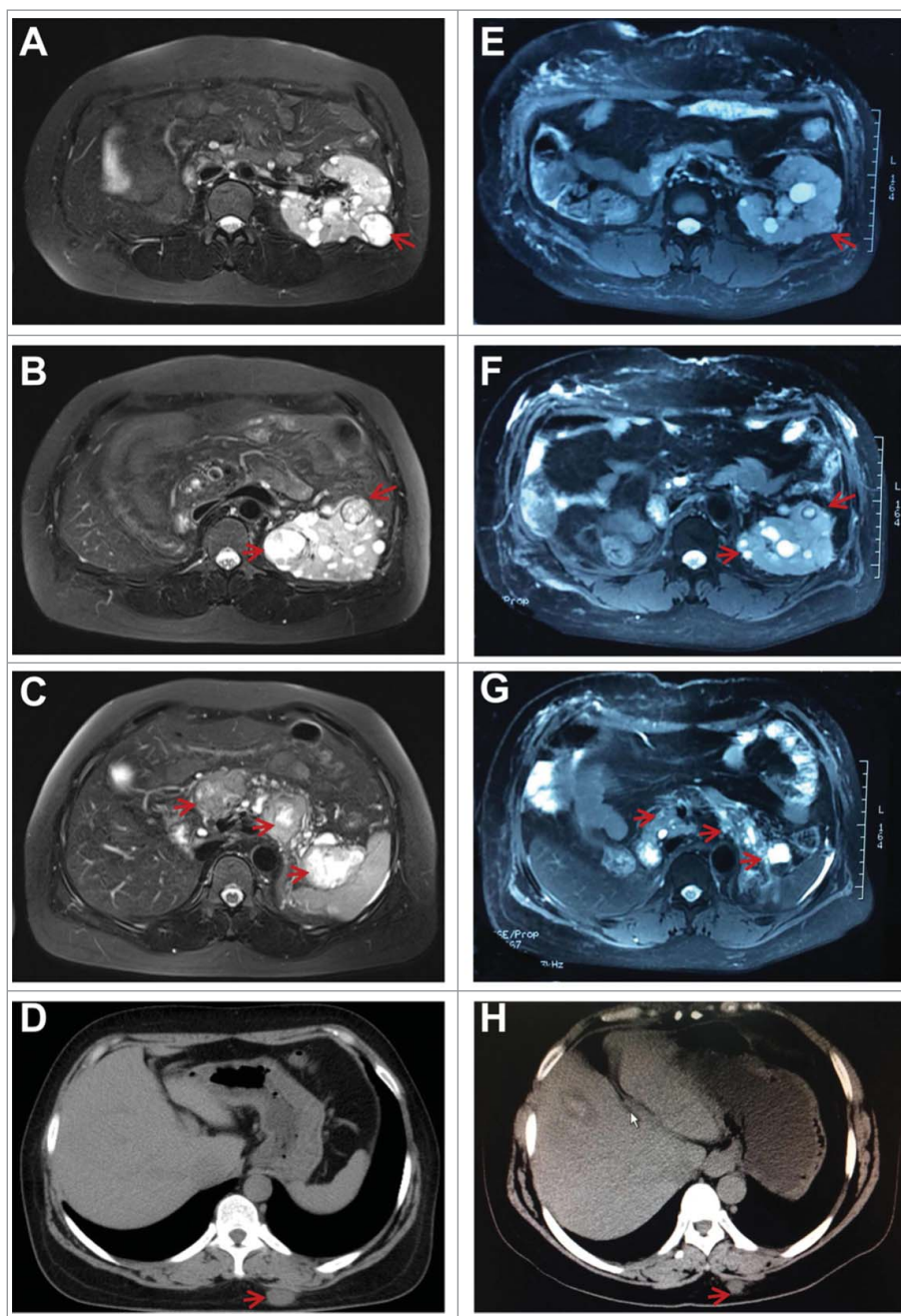


Figure 3. Magnetic resonance imaging (MRI) and computed tomography (CT) scans from Patient 3. The MRI scans show multiple RCCs in the left kidney including RCC in the dorsal of the kidney (A and E), ventral of the kidney and beside the spine (B and F), as well as three pancreatic lesions (C and G) before and after sunitinib treatment. The CT scans show the lesion on her back before and after sunitinib treatment (D and H). Red arrows indicate the masses.

Table 1. Characteristics of three patients with VHL disease.

Case No.	Age	Gender	VHL gene mutation	Phenotypes				Sunitinib	
				RCC	Pheo	HB	Pancreatic NET	Initial date	Dosage
1	44	Female	c. 239G>T; p. Ser80Ile	Right	Bilateral	Right cerebellum	Yes	May 2015	50 mg/day (4/2 scheme [*])
2	54	Male	c. 239G>T; p. Ser80Ile	Bilateral	Left	Bilateral cerebellum	—	January 2017	50 mg/day (4/2 scheme)
3	56	Female	c. 232A>T; p. Asn78Tyr	Bilateral	—	—	Yes	August 2011	37.5 mg/day (4/2 scheme)

^{*}4/2 scheme: Patients took the indicated dosage once per day for 4 weeks followed by a 2-week break across repeated cycles; VHL: Von Hippel-Lindau, RCC: renal cell carcinoma, Pheo: pheochromocytoma, HB: hemangioblastoma, NET: neuroendocrine tumor.

Table 2. Changes of the masses in the Patients.

Patients	Kind and/or Location of the Mass	Before sunitinib treatment	After sunitinib treatment
Patient 1	RCC	2.50 × 2.10 cm	1.10 × 0.90 cm
	Pheo	6.10 × 3.90 cm	3.30 × 2.40 cm
Patient 2 (RCC)	Renal hilus	6.33 × 5.55 cm	4.66 × 4.35 cm
	Lower ventral	5.67 × 3.89 cm	3.48 × 2.56 cm
	Dorsal	2.75 × 2.13 cm	1.19 × 0.68 cm
	Lower dorsal	3.64 × 3.12 cm	2.91 × 2.03 cm
	Superior pole	3.39 × 2.57 cm	2.41 × 1.88 cm
Patient 3	Dorsal RCC	2.84 × 2.40 cm	1.11 × 1.00 cm
	Ventral RCC	2.24 × 2.05 cm	0.96 × 0.95 cm
	RCC beside the spine	3.47 × 3.21 cm	0.90 × 0.84 cm
	Pancreas head	3.09 × 2.4 cm	1.79 × 1.70 cm
	Pancreas body	3.25 × 2.24 cm	1.84 × 1.05 cm
	Pancreas tail	3.45 × 3.38 cm	1.74 × 1.68 cm
	Mass on her back	2.22 × 1.32 cm	1.46 × 0.85 cm

RCC: renal cell carcinoma, Pheo: pheochromocytoma.

operative head CT scan confirmed complete resection of the tumor (Figure 1F). In Patient 2, all the masses in his right kidney decreased in size and iodine uptake after 4 months of sunitinib treatment (Figure 2E-H), as reported in Table 2. In Patient 3, the sizes of the RCCs in her left kidney and pancreatic lesions decreased, evidenced by the representative MRI scan after sunitinib treatment on August 2017 (Figure 3E-G), and remained stable through 6 years of follow-up. Interestingly, the sizes of the lesions on her back also decreased due to the treatment of sunitinib (Figure 3H). All the changes of the tumor sizes were concluded in Table 2.

Toxicity

All three patients reported adverse side effects to sunitinib treatment, including fatigue, diarrhea and mucositis (Table 3), but no severe toxic effects (i.e., grade 3–5) were observed in these patients.

Discussion

Our retrospective study identified three patients with confirmed VHL disease who exhibited positive clinical outcomes in response to sunitinib. These case studies indicate that sunitinib may be an effective treatment for VHL disease-related tumors.

To date, no VHL-targeted drugs have been approved by the FDA for the treatment of VHL-related tumors. Several treatments are available, however, that target molecules downstream of VHL. Several of these treatments, including VEGF monoclonal antibodies, tyrosine kinase inhibitors (TKI), and mechanistic target of rapamycin (mTOR) inhibitors, have been shown to be effective for the treatment of VHL-related tumors.⁷ Of note, TKIs are currently used to treat advanced renal cancer, and recently have been used to treat pancreatic neuroendocrine tumors. In clinical studies of patients with advanced cRCC, 40% of cases exhibited a partial response and up to 90% of cases exhibited stable disease on TKIs.⁸ Previous studies have reported that the effectiveness of VEGF-targeted agents may be associated with the patient's VHL inactivation status, as patients with loss-of-function mutations (i.e., frameshift, nonsense, splice, and in-frame deletions/insertions) had a better

Table 3. Treatment-emergent adverse side effects.

Toxicity	Grades of the toxicity		
	Patient 1	Patient 2	Patient 3
Fatigue	2	1	2
Diarrhea	1	—	1
Mucositis	—	—	2 (gastric)
Anemia	2	—	—
Hand/foot/skin reaction	2	1	1
Rash	—	—	—
Nausea	1	—	1
Neutropenia	1	—	1
Dysgeusia	1	—	—
Sensory neuropathy	—	—	—
Vomiting	—	—	1
Skin rash	1	—	—
Dyspnea	—	—	—
Edema (head and neck)	1	1	1
Hypertension	—	1	2
Pain	—	—	—
Headache	—	—	—
Anorexia	1	—	1
Hypophosphatemia	—	—	—
Epiphora	—	—	1
Transaminitis	—	—	—
Alopecia	2	1	1
Infection	—	—	—
Hyperbilirubinemia	—	—	1
Cough	—	—	—
Dysphagia	—	—	—
Confusion	1	—	1
Elevated creatinine	—	—	2
Epistaxis	—	—	—

response rate than those with wild-type *VHL*.^{9,10} Our three patients had mutations associated with an inactivated VHL protein, and all three patients, especially Patient 1, responded positively to sunitinib treatment.

Several previous pilot and small retrospective studies have indicated that sunitinib, which is a common TKI in China, may be effective for the treatment of VHL disease-related tumors, which is consistent with the findings from our small retrospective case study. A Phase-II trial by Jonasch et al. that evaluated the effect of sunitinib on 18 RCCs and 21 hemangioblastomas among 15 patients with VHL disease reported partial response in six (33%) of the RCCs but none of the hemangioblastomas, and disease control (i.e., partial response + stable disease) in 90% of the RCCs and 91% of the hemangioblastomas.⁸ Kim et al. reported that VHL-related metastatic RCC is highly responsive to VEGF TKI for a prolonged period of time, and suggested that benign cysts or tumors associated with VHL disease also could be controlled with VEGF TKIs.⁷ A multicenter, Phase-II, open-label study of sunitinib from the PREDIR VHL network has shown that all five enrolled patients with VHL disease exhibited stable disease as the best response at 6 months. This study also showed that sunitinib was more effective for VHL-related RCCs than for other VHL-related lesions.¹¹ More recently, a retrospective study by Roma et al. showed that 9 of 14 (64%) patients with VHL who received sunitinib treatment as a first-line therapy exhibited radiological response not only in renal and hepatic lesions but also in pancreatic nodules.¹² In addition, a case study reported that sunitinib may be effective in treating a patient with primitive neuroectodermal tumors that express a copy number loss of the VHL gene.¹³

According to these previous studies, however, sunitinib may not be equally effective across all VHL disease-associated lesions. In 2009, Jimenez et al. reported that a carrier of a *VHL* germline mutation with an aggressive malignant pheochromocytoma and several RCCs and pancreatic neuroendocrine tumors exhibited decreases in the sizes of most tumors after 6 months of treatment with sunitinib.¹⁴ Furthermore, several other studies^{7,8,11,15} have shown that sunitinib may be more effective in cRCCs arising from patients with VHL disease compared to sporadic non-VHL-related RCCs. Previous studies are equivocal, however, with respect to the effects of sunitinib on other VHL-related lesions. For example, Kim et al., but not other studies, found that sunitinib may control the growth of lesions in the pancreas and cerebellum. Knickelbein et al. found that treatment with sunitinib improved hemangioblastoma-related retinal edema in patients with VHL-related retinal hemangioblastomas, but did not improve their visual acuity or reduce the size of the tumor.¹⁶ In contrast, Roma et al. recorded radiological responses to sunitinib in renal, pancreatic, adrenal, hepatic, pulmonary, and subcutaneous tumors but not in hemangioblastomas.¹² A recent study reported that sunitinib was effective in pancreatic neuroendocrine tumors associated with VHL.¹⁷ In our three patients, sunitinib treatment was associated with decreases in RCC size and may also have effects on VHL-related pheochromocytomas and hemangioblastomas, as well as pancreatic NET. These discrepancies across studies may be due to differences in individuals, mutations, and/or tissues, which in turn may be associated with differential expressions of VEGF and therefore diverse responses to sunitinib.

Other agents that target molecules downstream from VHL have been used for the treatment of VHL-related tumors. In the study by Kim et al., for example, patients responded to treatment with the mTOR inhibitor, everolimus, after not responding to a VEGF TKI; moreover, one patient exhibited a partial response to sorafenib after her disease progressed on sunitinib and everolimus.⁷ Choi et al. also reported on two patients with VHL disease who were treated effectively with sorafenib.¹⁸ Furthermore, two small non-controlled prospective clinical trials investigating the effects of pegaptanib and ranibizumab on the treatment of VHL-associated retinal capillary hemangioblastomas have shown that these drugs might reduce exudation without any evidence for tumor repression.^{19,20} In addition, Metelo et al. have demonstrated that the HIF2a inhibitor, lead compound 76, can inhibit zebrafish orthologs of human HIF2a and ameliorate phenotypic abnormalities in *vhl*^{-/-} embryos, indicating that HIF2a inhibitors may be effective for treating VHL disease-related abnormalities.²¹ Further studies are needed to determine whether these agents are suitable for treatment of patients with VHL disease.

Although our study and previous studies are limited by small numbers of patients, together their results suggest that sunitinib may be an effective treatment in patients with VHL disease. Further evaluation of sunitinib in patients with VHL disease is warranted. It also will be important to examine the role of the VHL/HIF pathway in sporadic RCCs, pheochromocytomas, and hemangioblastomas, and to examine whether we can better select drugs that target these tumor types.

Materials and methods

Study design

We performed a retrospective analysis of clinical and radiological data from approximately 20 patients with VHL disease from five families. Three of these patients with multiple RCCs as well as Pheos or paragangliomas were treated with sunitinib. We retrospectively compared changes in their VHL disease-associated tumors before and after sunitinib treatment.

Compliance with ethical standards

All procedures involving human participants were carried out in accordance with the 1964 Declaration of Helsinki. The Daping Hospital of the Third Military Medical University waived institutional review board approval for the study; however, written informed consent for the use of medical records and related images was obtained from each patient.

Treatment

According to all the patients' disease status, sunitinib was prescribed to these patients by the professional urologist. All three patients received oral sunitinib once per day for 4 weeks, followed by 2 weeks with no treatment (4/2 scheme). The starting dose of sunitinib was 50 mg/day. If side effects were severe, however, the daily dose was reduced to 37.5 mg. After one cycle, the treatment was continued unless the side effects became unacceptable or the progression of the disease occurred.

Clinical evaluation of responses to sunitinib

A computed tomography (CT) or magnetic resonance imaging (MRI) scan was extracted from each medical record prior to treatment with sunitinib to evaluate the VHL disease-associated tumors. Scans taken after sunitinib treatment also were extracted from the medical record to evaluate changes in the tumors. The adverse side effects associated with sunitinib also were assessed according to NCI-CTC v3.0 criteria.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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