Published in final edited form as:

Target Oncol. 2012 June ; 7(2): 145–149. doi:10.1007/s11523-012-0214-0.

Pazopanib therapy for cerebellar hemangioblastomas in von Hippel–Lindau disease

Betty Y. S. Kim,

Department of Neurosurgery, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 442, Houston, TX 77030, USA

Eric Jonasch, and

Department of Genitourinary Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Ian E. McCutcheon

Department of Neurosurgery, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 442, Houston, TX 77030, USA

Ian E. McCutcheon: imccutch@mdanderson.org

Abstract

von Hippel–Lindau (VHL) disease is a genetically acquired multisystem tumor syndrome of the viscera and central nervous system (CNS). The most common tumors associated with this disease are histologically benign, slow-growing CNS hemangioblastomas affecting the retina, cerebellum, brainstem, spinal cord or nerve roots. With mean age at diagnosis of 30 years, CNS hemangioblastomas are usually the first manifestation of the disease. Ongoing clinical and radiological surveillance is required, with symptomatic lesions necessitating treatment. As tumor growth is inevitable during the lifetime of most VHL patients, and the multiplicity of tumors may preclude surgical cure, the search for effective therapies is ongoing. Here we provide the first report demonstrating clinical and radiological anti-tumor response using pazopanib, a small molecule multi-receptor tyrosine kinase inhibitor, in a patient with treatment-refractory VHL-associated CNS hemangioblastoma. Treatment initiation with daily oral pazopanib (800 mg/day) resulted in significant neurologic improvement and radiologic tumor volume reduction.

Keywords

Von Hippel–Lindau disease; Hemangioblastoma; Pazopanib

Introduction

von Hippel–Lindau (VHL) disease is an autosomal dominant inherited cancer syndrome characterized by a germ line mutation in the *VHL* tumor suppressor gene [1-3]. This mutation leads to the development of tumors in a variety of organs and tissues, including central nervous system (CNS) hemangioblastomas, renal cell carcinomas (RCCs) and cysts,

endolymphatic sac tumors, pheochromocytomas, pancreatic neuroendocrine tumors, and epididymal cystadenomas. VHL disease has a reported incidence of one in 39,000 live births and penetrance >90% [1]. Its most common manifestation is CNS hemangioblastoma, found in 60–80% of all VHL patients [1, 4]. These tumors can arise anywhere along the neural axis with the majority localized in the cerebellum and spinal cord [1-3].

Despite their benign histology, CNS hemangioblastomas can cause significant morbidity during the lifetime of VHL patients, and require multi-modal therapies that include surgical resection, pharmacotherapy, and irradiation [2, 5]. Management strategies are tailored individually based on clinical and radiological progression. If surgically accessible, most symptomatic hemangioblastomas are resected [2, 5]. Despite the unpredictable growth pattern of these tumors, the overall management goal for asymptomatic hemangioblastomas is avoidance of unnecessary surgical interventions, while maintaining neurologic status as long as possible with close clinical monitoring [1, 3, 5]. For symptomatic lesions in eloquent or surgically inaccessible regions, therapeutic planning must consider tumor size, location, multiplicity, and presence of associated cystic component. For small inaccessible lesions without a perilesional cyst, stereotactic radiosurgery is sometimes used. However, it is not clear whether stability of tumor size following radiosurgery can truly be attributed to treatment effect or whether it simply reflects the natural history of hemangioblastoma that includes unpredictable periods of rapid tumor expansion between periods of tumor quiescence [1]. Pharmacologic agents such as anti-angiogenic agents, EGFR tyrosine kinase inhibitors (erlotinib), interferon- α -2a, and VEGFR2 inhibitors (SU5146), have produced suboptimal clinical responses [6-9].

Pazopanib, an orally administered multi-tyrosine receptor kinase blocker, has been used to treat RCC, another tumor commonly found in VHL disease [10]. The anti-tumor effects of pazopanib are thought to arise from inhibition of tumor vascularization by antagonism of multiple pro-angiogenic receptors including vascular endothelial growth factor receptors (VEGFR-1, -2, -3), platelet-derived growth factor receptors (PDGFR- α , - β), and a cytokine receptor (Kit) [1, 2]. Under normal physiological conditions, these receptor expression levels are tightly regulated by hypoxia-inducible factor-1 α (HIF), which is in turn controlled by VHL and mammalian target of rapamycin (mTOR) proteins [1, 10, 11]. VHL protein dysfunction inhibits degradation of HIF transcriptional complex and causes a rise in HIF levels resulting in the up-regulation of multiple factors promoting angiogenesis and vasculogenesis, including EGF, PDGF, and erythropoietin [1, 2]. In combination with loss of anti-tumor function of the VHL protein, these events promote the overgrowth of the highly vascularized tumors associated with VHL disease. Clinical evidence supports the effectiveness of pazopanib in treatment of RCCs, and its actions downstream within the VHL regulation pathway suggest that this drug could also be useful in VHL-associated hemangioblastomas unsuitable for surgical or radiation therapy [10, 12]. Here, we report the first case in which pazopanib therapy caused significant clinical and radiological improvement in a VHL patient with treatment-refractory CNS hemangioblastoma.

Clinical history

A 47-year-old African-American male was referred to MD Anderson Cancer Center in 2006 for treatment-refractory hemangioblastoma in both cerebellar hemispheres. Diagnosed with VHL at the age of 18, he had undergone six prior craniotomies for multiple symptomatic cerebellar hemangioblastomas, gamma knife radiosurgery for one cerebellar tumor, and limited-field irradiation of several hemangioblastomas within the cervical spinal cord. After the diagnosis of VHL disease was made by clinical criteria, genetic testing showed heterozygous deletion at nucleotide 471 with a translation frame shift of mRNA to a premature stop codon at position 158. By the time he was seen at MD Anderson, he was dependent on a walker for ambulation due to progressive gait ataxia and had developed significant dysarthria and difficulty swallowing as hemangioblastoma growth continued. With clinical and radiological progression, this patient was enrolled in a clinical trial of stereotactic radiosurgery in 2006. Because the treated cerebellar tumor continued to grow after radiosurgery, he had resection of this symptomatic hemangioblastoma in 2008. During the same year, abdominal CT revealed new bilateral renal masses consistent with multifocal RCC. With progression of the cerebellar and renal masses, he was placed on sunitinib (SU11248), a multi-receptor tyrosine kinase inhibitor. However, this therapy was aborted due to the development of severe neutropenia and absence of therapeutic response in CNS and retinal tumors while on treatment. He had worsening of the visual acuity in his right eye due to progression of retinal hemangioblastoma, and required cryotherapy in 2008.

Over time, this patient became significantly more ataxic, had several falls associated with fractures, and became wheelchair-dependent. With limited options available, he was started on pazopanib therapy (800 mg/day) in February 2010, with monitoring of liver and hematological functions. Within 4 weeks of pazopanib therapy, his family observed marked clinical improvement in his speech and swallowing. At his last follow-up in July 2011, his dysarthria, hoarseness of voice, and swallowing function had improved significantly and he had regained ambulation for short distances. Magnetic resonance imaging (MRI) performed in July 2011 revealed significant reduction in the size of his several symptom-producing cerebellar hemangioblastomas (Fig. 1). Tumor volumes before and after treatment are shown in Fig. 2. The volume of the largest lesion was reduced by 54% since the initiation of pazopanib therapy. Several small, asymptomatic lesions showed reduction in tumor volumes (25–60%). Pazopanib therapy also slowed the growth rate of visceral masses including those in the kidney and pancreas. Mild adverse reactions associated with pazopanib included transient diarrhea and oral mucosal ulcerations. Our patient also developed hypertension requiring amlodipine (5 mg/day) with good blood pressure control. At present, he remains moderately neutropenic but has not experienced clinical sequelae of neutropenia-related opportunistic infections. His liver function tests remain normal. The patient remains on the same dose of pazopanib with ongoing neurologic improvement 19 months after starting treatment.

Discussion

We report a patient with VHL disease who presented with progressive cerebellar hemangioblastoma growth causing significant morbidity despite multiple surgical and

radiotherapeutic interventions. With significant and ongoing decline in his quality of life from moderate bulbar dysfunction and severe gait ataxia with wheelchair dependency, pazopanib therapy was initiated after he had exhausted other recommended therapeutic options. While the exact mechanism of hemangioblastoma pathogenesis in VHL disease remains incompletely understood, it is clear that elevation of HIF signaling plays an important role in this process [1, 2]. Acting as a transcription factor, HIF normally increases expression of pro-angiogenic factors, which results in enhanced vascularization and tissue perfusion in response to hypoxic conditions. In combination with mTOR, VHL protein regulates HIF levels by mediating its degradation [2]. In VHL disease, the dysfunction of VHL protein leads to upregulation of HIF and significant elevation of VEGF, PDGF, and other pro-angiogenic factor expression. These events increase the proliferation of endothelial cells and pericytes and induce formation of the highly vascularized tumors associated with VHL disease [1, 2].

Anti-angiogenic agents including small molecule and monoclonal antibody-based tyrosine kinase inhibitors have demonstrated effectiveness against other VHL-related tumors, including RCCs [10]. Humanized monoclonal antibodies such as bevacizumab, and small molecule kinase inhibitors (sunitinib, sorafenib, pazopanib) are recommended by the US National Comprehensive Cancer Network as the first-line treatment for stage IV clear cell renal carcinomas or unresectable tumors [12]. Similarly, the European Association of Urology has recommended pazopanib as the preferred treatment for metastatic RCC following cytokine therapy [10, 12]. A recent prospective study demonstrated differential responsiveness of VHL-associated lesions to sunitinib therapy [9]. In patients harbouring RCCs, CNS hemangioblastomas and other VHL-associated lesions, RCC size reduction was most significant following sunitinib therapy with little or no effect on CNS hemangioblastomas [9]. In the treatment of other highly vascularized CNS malignant tumors, anti-angiogenic agents have produced mixed results. Bevacizumab, a monoclonal antibody that inhibits VEGF-A, and cediranib, a pan-VEGFR tyrosine kinase inhibitor with anti-PDGFR- α , PDGFR- β , and c-Kit activities have achieved progression-free survivals of 29% and 28%, respectively, at 6 months in adults with recurrent glioblastomas [13, 14]. However, a phase II clinical trial using pazopanib in glioblastoma did not show an increase in progression-free survival despite an in situ biological response observed on MRI [15]. Because hemangioblastomas are caused by a VHL gene mutation, which leads not only to overexpression of VEGF, but also heightens PDGF signaling, these tumors could respond to treatment with a pan-VEGFR inhibitor with anti-PDGFR activity as well. Although our patient demonstrated stabilization with sunitinib therapy, a significant response to pazopanib was observed. Evaluation of the kinase inhibition profiles of both sunitinib and pazopanib reveal greater inhibitory effects of pazopanib for fibroblast growth factor receptor (FGFR) [16, 17]. Interestingly, the endothelial angiogenic receptor profiles in hemangioblastomas and RCCs demonstrated greater FGFR activation in hemangioblastomas compared to RCCs [9]. Therefore, pazopanib may be a more suitable candidate for targeting hemangioblastomas.

We suspect that the clinical improvements in our patient following pazopanib treatment, although not completely understood, can be attributed to the anti-angiogenic effects of pazopanib *via* decreased proliferation of endothelial cells and pericytes. Given that

hemangioblastomas are highly vascular, targeting VEGFR can potentially cause growth arrest and regression of tumors while reducing the degree of hemangioblastoma-associated cerebral edema [18]. MRI showed significant reduction (25–60%) in tumor volume of CNS hemangioblastomas of varying sizes, with the largest lesion demonstrating 54% volume reduction with pazopanib treatment. This reduction correlates with the improvement of this patient's speech and swallowing functions. By inhibiting proliferation of endothelial cells and pericytes, pazopanib exerts its anti-tumor effects through limiting the vascularization needed for sustained tumor growth [12]. Furthermore, unlike traditional cytotoxic agents, pazopanib and other anti-VEGF agents augmented their therapeutic benefit by reducing the vasogenic edema often associated with CNS tumors [15]. It has been suggested that anti-VEGF agents can reduce the heterogeneity and permeability of tumor vasculature, and reestablish the normal pressure gradients between intravascular and interstitial spaces [14, 19]. Decrease in vasogenic edema often leads to improved neurological function, as observed in patients with high grade glioma who are treated with cediranib [14]. Finally, reducing blood flow within these tumors may reverse local vascular steal, with improvement of function in adjacent regions of brain in which flow has been restored.

In our patient, baseline evaluation was performed during each clinic visit, and included a complete medical history, physical examination including a full neurologic status, Karnofsky performance status, and hematological and liver function tests. Surveillance MR imaging of the brain and spine was also performed. Marked decreases in vascular permeability and vasogenic edema were inferred by the significant reduction in tumor enhancement following gadolinium administration on T1-weighted imaging and T2-weighted signal changes on fluid attenuated inversion recovery (FLAIR) MR sequences, respectively [20] (Fig. 1). In our patient, the radiological response to pazopanib therapy correlated directly with improved clinical status.

Pazopanib has demonstrated a favorable tolerance profile in patients with RCC or glioblastoma, with most adverse effects of grade 1 or 2 severity, using the National Cancer Institute Common Toxicity Criteria (version 4.0). The most commonly experienced adverse events of pazopanib include diarrhea, nausea, vomiting, anorexia, hypertension, and hair color changes [12]. With the exception of his development of severe neutropenia, our patient experienced only mild adverse events (grades 1 and 2). Mild hypertension, fatigue, oral mucosal ulcerations, and diarrhea were the main non-hematological toxicities in our patient. Leukopenia, neutropenia, thrombocytopenia, and lymphocytopenia have also been reported in >30% of patients treated with pazopanib, possibly due to the inhibition of c-kit, and to a lesser extent fms-like tyrosine kinase-3 (flt-3), as both are important in the proliferation and differentiation of bone marrow hematopoietic stem cells and progenitor cells [21]. Prior to the initiation of pazopanib, our patient's baseline neutrophil count was 2 K/ μ l (normal range: 1.7–7.3 K/ μ l) with 51% of his total cell count (normal range: 42–62%) attributed to neutrophils. While on pazopanib therapy, our patient remains neutropenic at 0.87 K/ μ l with 30% of his total blood cells attributed to neutrophils. Other cellular components of the bone marrow such as erythrocytes, leucocytes, and platelets have been consistently normal. At present, our patient continues on a stable dose of pazopanib with no evidence of opportunistic infection. Finally, hepatotoxicity is another potential concern with pazopanib administration. In a recent study, close to 50% of patients receiving pazopanib experienced

elevated alanine aminotransferase and aspartate aminotransferase levels and approximately 40% had elevated total bilirubin levels when compared to a placebo group [12]. In our patient, however, we did not observe any abnormalities in hepatic function.

In conclusion, we report here the first successful use of pazopanib, a pan-VEGFR, PDGFR, and c-kit tyrosine kinase inhibitor, for the management of treatment-refractory VHL-associated cerebellar hemangioblastoma. With continued therapy, the patient displayed a moderate clinical response with improvements in his speech and swallowing functions. While pazopanib is effective in the management of other tumors such as RCCs, this is the first time that this (or indeed any) agent has demonstrated clinical benefit for CNS hemangioblastomas. The experience gathered from this patient provides new insights into the management of other highly vascularized tumors, especially those who lack other treatment options.

Acknowledgments

The authors thank Miao Li for performing manual segmentation on tumor images and volumetric analysis for this study. We thank Dr. Dawid Schellingerhout for assistance in technical discussions on brain imaging techniques.

References

1. Butman JA, Linehan WM, Lonser RR. Neurologic manifestations of von Hippel–Lindau disease. *JAMA*. 2008; 300:1334–1342. [PubMed: 18799446]
2. Lonser RR, Glenn GM, Walther M, Chew EY, Libutti SK, Linehan WM, Oldfield EH. von Hippel–Lindau disease. *Lancet*. 2003; 361:2059–2067. [PubMed: 12814730]
3. Wanebo JE, Lonser RR, Glenn GM, Oldfield EH. The natural history of hemangioblastomas of the central nervous system in patients with von Hippel–Lindau disease. *J Neurosurg*. 2003; 98(1 Suppl): 82–94. [PubMed: 12546356]
4. Hes FJ, van der Luijt RB, Lips CM. Clinical management of von Hippel–Lindau (VHL) disease. *Neth J Med*. 2001; 59:225–234. [PubMed: 11705642]
5. Ammerman JM, Lonser RR, Dambrosia J, Butman J, Oldfield EH. Long-term natural history of hemangioblastomas in von Hippel–Lindau disease: implications for treatment. *Clin Neurosurg*. 2006; 53:324–331. [PubMed: 17380770]
6. Rogers LR, LoRusso P, Nadler P, Malik G, Shields A, Kaelin W. Erlotinib therapy for central nervous system hemangioblastomatosis associated with von Hippel–Lindau disease: a case report. *J Neuro Oncol*. 2011; 101:307–301.
7. Niemela M, Maenpaa H, Salven P, Summanen P, Poussa K, Laatikainen L, Jaaskelainen J, Joensuu H. Interferon-2a therapy in 18 hemangioblastomas. *Clin Cancer Res*. 2001; 7:510–516. [PubMed: 11297241]
8. Madhusudan S, Deplanque G, Braybrooke JP, Cattell E, Harris AL. Antiangiogenic therapy for von Hippel–Lindau disease. *JAMA*. 2004; 291:943–944. [PubMed: 14982909]
9. Jonasch E, McCutcheon IE, Waguespack SG, Wen S, Do KA, Davis DW, Zhang Y, Smith L, Tamboli P, Tannir NM, Gombos DS, Fuller GN, Matin SF. Pilot trial of sunitinib therapy in patients with von Hippel–Lindau disease. *Ann Oncol*. 2011 accepted.
10. Gore ME, Larkin JMG. Challenges and opportunities for converting renal cell carcinoma into a chronic disease with targeted therapies. *Br J Cancer*. 2011; 104:399–406. [PubMed: 21285971]
11. Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. *Nature*. 2011; 473:298–307. [PubMed: 21593862]
12. Sanford M, Keating GM. Pazopanib. *BioDrugs*. 2010; 24:279–286. [PubMed: 20649181]
13. Friedman HS, Prados M, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WK, Paleologos N, Nicholas Mk, Jensen R, Vredenburgh J, Huang J, Zheng M, Cloughesy T. Bevacizumab alone and

- in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol.* 2009; 28:4733–4740. [PubMed: 19720927]
14. Batchelor T, Duda DG, di Tomaso E, Ancukiewicz M, Plotkin SR, Gerstner E, Eichler AF, Drappatz J, Hochberg FH, Benner T, Louis DN, Cohen KS, Chea H, Exarhopoulos A, Loeffler JS, Moses MA, Ivy P, Sorensen AG, Wen PY, Jain RK. Phase II study of cediranib, an oral pan-endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. *J Clin Oncol.* 2010; 28:2817–2823. [PubMed: 20458050]
 15. Iwamoto FM, Lamborn KR, Robins I, Mehta MP, Chang SM, Butowski NA, DeAngelis LM, Abrey LE, Zhang WT, Prados MD, Fine HA. Phase II trial of pazopanib (GW786034), an oral multi-targeted angiogenesis inhibitor, for adults with recurrent glioblastoma (North America Brain Tumor Consortium Study 06-02). *Neuro-Oncology.* 2010; 12:855–861. [PubMed: 20200024]
 16. Bukowski RM. Pazopanib: a multikinase inhibitor with activity in advanced renal cell carcinoma. *Expert Rev Anticancer Ther.* 2010; 10:635–645. [PubMed: 20469994]
 17. Mendel DM, Laird D, Xin X, Cherrington JM. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic pharmacodynamic relationship. *Clin Cancer Res.* 2003; 9:327–337. [PubMed: 12538485]
 18. Kaal EC, Vecht CJ. The management of brain edema in brain tumors. *Curr Opin Oncol.* 2004; 16:593–600. [PubMed: 15627023]
 19. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science.* 2005; 307:58–62. [PubMed: 15637262]
 20. De Groot JF, Fuller G, Kumar AJ, Piao Y, Eterovic K, Ji YJ, Conrad CA. Tumor invasion after treatment of glioblastoma with bevacizumab: radiographic and pathologic correlation in humans and mice. *Neuro-Oncology.* 2010; 12:233–242. [PubMed: 20167811]
 21. Kumar R, Crouthamel MC, Rominger DH, Gontarek RR, Tummino PJ, Levin RA, King AG. Myelosuppression and kinase selectivity of multikinase angiogenesis inhibitors. *Br J Cancer.* 2009; 101:1717–1723. [PubMed: 19844230]

Fig. 1.

Representative magnetic resonance images from a patient with VHL disease on pazopanib therapy. Axial, coronal, sagittal T1-weighted images (post-contrast) and T2-weighted images with fluid-attenuated inversion recovery sequence (*FLAIR*) 3 weeks before treatment (**a–d**) and 19 months after starting pazopanib (**e–h**). These demonstrate decreasing tumor volume, contrast enhancement and vasogenic edema over time. All images are displayed per standard radiographic convention

Fig. 2.

Evaluation of radiologic responsiveness of von Hippel–Lindau (VHL)-associated CNS hemangioblastomas to pazopanib therapy. Five hemangioblastomas (**a–e**) were assessed in a VHL patient on pazopanib therapy. Tumor volume reduction shows moderate responsiveness to pazopanib with the largest symptomatic lesion (**a**) decreasing in volume by 54% (*left graph*). This reduction in tumor volume correlated directly with improved bulbar and cerebellar functions. Corresponding absolute tumor volumes pre- and post- pazopanib treatment are also shown (*right table*). Tumor volumetric assessment was conducted using Vitrea2 software (version 2.2; Vital images, Plymouth, MN). MR image area corresponding to the hemangioblastoma showing contrast enhancement was manually segmented to delineate tumor-specific pixels across all sections