Attainment of a Long-term Favorable Outcome by Sunitinib Treatment for Pancreatic Neuroendocrine Tumor and Renal Cell Carcinoma Associated with von Hippel-Lindau Disease


Abstract

von Hippel-Lindau (VHL) disease, caused by germline mutations in the VHL gene, is a hereditary autosomal-dominant disorder which predisposes the individual to various malignant and benign tumors. VHL acts as a tumor suppressor, mainly through the negative regulation of hypoxia-inducible factors. Molecular-targeted drugs against vascular endothelial growth factor-signaling pathways, a target of hypoxia-inducible factors, have recently been introduced into clinical practice for the treatment of patients with sporadic renal cell carcinoma and pancreatic neuroendocrine tumors. However, whether such treatments are effective in patients with VHL disease remains to be elucidated. We herein report a Japanese patient with VHL disease who was successfully treated with sunitinib for approximately 5 years.

Key words: sunitinib, pancreatic neuroendocrine tumor, renal cell carcinoma, von Hippel-Lindau disease


Introduction

von Hippel-Lindau (VHL) disease is a hereditary autosomal-dominant tumor syndrome characterized by the occurrence of multiple malignant and benign tumors of various organs, including retinal hemangioma, hemangioblastoma of the central nervous system, pancreatic neuroendocrine tumor or cystadenoma, pheochromocytoma, and clear cell renal cell carcinoma (RCC) (1, 2). VHL disease is caused by germline mutations in the VHL gene, which is located on chromosome 3p25-26. The VHL protein exerts tumor-suppressive functions, mainly by directly regulating hypoxia-inducible factors (HIFs) such as HIF-1α and HIF-2α through ubiquitylation and proteasomal degradation (3). Mutated VHL loses its ubiquitin ligase activity, resulting in an increased intracellular level 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)-β-related pathways (3). Moreover, somatic mutations or promoter methylation in the VHL gene, along with the loss of heterozygosity in the VHL locus, are observed in more than 90% of patients with sporadic clear cell renal cell carcinoma (RCC), according to a recent comprehensive molecular analysis (4). Thus, loss-of-function alterations in VHL contribute to the process of carcinogenesis of VHL disease, as well as most sporadic cases of clear cell RCC.

For recurrent or unresectable RCC, therapeutic outcomes obtained through classical cytokine therapies, such as interferon-α and interleukin-2 therapies, have been limited. Recently, based on the causative role of activation of the...
VEGF pathway in the pathogenesis of RCC, molecular-targeted therapies against components of the VEGF pathway have been developed for the treatment of sporadic RCC. Tyrosine kinase inhibitors that target VEGFRs, such as axitinib (5), sorafenib (6), sunitinib (7), and pazopanib (8); mammalian target of rapamycin (mTOR) inhibitors, such as everolimus and temsirolimus; and a monoclonal anti-VEGF antibody, bevacizumab (9), are currently available in the USA for treating patients with sporadic RCC. Moreover, sunitinib and an mTOR inhibitor, everolimus, have been incorporated into clinical use for patients with pancreatic neuroendocrine tumors (10, 11). However, due to the rarity of VHL disease, there are few large and prospective studies analyzing the efficacies of drug therapies in patients with VHL disease. Thus, it remains to be clarified whether treatments with such targeted therapies against the VEGF signaling pathway are similarly effective for patients with VHL disease-associated tumors.

We herein report the case of a Japanese patient with VHL disease who was successfully treated with sunitinib for approximately 5 years.

### Case Report

A 19-year-old man experienced abnormal vision in his right eye and consulted an ophthalmologist. Consequently, he was found to have retinal angiomatosis of his right eye. At 23 years of age, he experienced abnormal vision in his left eye and presented to the Department of Ophthalmology in our hospital. He repeatedly received retinal cryopexy for both eyes between 23 and 24 years of age. When he was 24 years of age, he suffered paralysis of the upper and lower limbs on his right side. At 25 years of age, he was again referred to our hospital due to deteriorating paralysis, and a computed tomography (CT) scan and magnetic resonance imaging detected tumors in a number of organs, including the spinal cord, kidney, pancreas, and liver. According to his present condition and his family history, as mentioned below, he was diagnosed with VHL disease. The research project was approved by the Ethical Committee of Tohoku University Graduate School of Medicine, and we obtained informed consent from the patient to perform a direct sequencing analysis for the VHL gene in the patient’s germline DNA, obtained from his peripheral leucocytes. The genetic analysis detected a germline missense mutation in the VHL gene (c. 233 A>G; p.N78S). Because codon 78 is located within the HIFα-binding domain, and this is one of the recurrently reported mutations in patients with VHL disease (12), this mutation was considered to be a pathogenic mutation, further corroborating the diagnosis of VHL disease. Tumors of the spinal cord in C1 and C2 were surgically resected and pathological examinations revealed that the tumors were hemangioblastomas. Three months later, tumors of the pancreatic body and tail were also surgically resected. The pathological findings revealed a neuroendocrine tumor of the pancreas (mitotic count: 1/10 high-power field, Ki67 index: 12%, G2, according to the WHO 2010 classification (13), Fig. 1A). After a 10-month follow-up, multiple liver tumors (3.5 mm in S2, 4 mm in S3, 28 mm and 18 mm in S4, 12 mm and 6 mm in S6, and 21 mm and 18 mm in S6-7) were subsequently resected because of their increased size, and the pathological examination revealed metastasis of the pancreatic neuroendocrine tumors to the liver (mitotic count: 1/10 high-power field, Ki67 index: 20%, G2, according to the WHO 2010 classification, Fig. 1B). Radiofrequency ablation was added to the two residual liver metastases in S2 and S3. Due to the presence of the other two tumors in S7, temozolomide (200 mg/body, day 1-5, q4w) was administered for three cycles, however, this treatment unfortunately resulted in further progression of the tumors. Thereafter, transcatheter arterial chemoembolization using 40 mg of epirubicin and 10 mL of lipiodol, an ethyl ester of iodinated poppy-seed oil fatty acid, was performed. Nevertheless, the S7 metastases further enlarged and new liver metas-
tases occurred (Fig. 2A). The patient was then referred to the Department of Medical Oncology in our hospital to receive systemic drug therapy.

As shown in Fig. 3, his mother had pancreatic and renal cysts at 37 years of age and retinal angiomatosis at 47 years of age. His maternal grandmother lost her eyesight and died from renal cancer and brain tumors at 58 years of age. According to his family history, the patient was considered to carry type I VHL disease (3).

As a first-line therapy, the patient started taking sorafenib 800 mg/day orally. Ten days after beginning the treatment, his treatment was stopped because of the side effect of a grade 3 erythema multiforme rash. As a second-line therapy, he successfully continued taking sunitinib 50 mg/day orally (day 1-28, every 6 weeks), with grade 2 toxicities such as hand-foot syndrome, diarrhea and stomatitis. For the treatment of this patient, we selected this dose, which is the standard regimen for RCC, because the patient had both RCC and pancreatic neuroendocrine tumors and because sunitinib at a 37.5 mg/day schedule had not yet been approved for treatments of pancreatic neuroendocrine tumors in Japan when the patient began receiving sunitinib treatment. Three months later, the sum of the diameter of the two liver tumors decreased from 67.9 (42.4+25.5) mm to 52.1 (35.0+17.1) mm, a 23% reduction. The size of the renal tumor changed from 17.3 mm to 12.0 mm, a 31% reduction. According to the response evaluation criteria in solid tumors (RECIST) version 1.1 (14), the response evaluation of the liver and renal tumors were stable disease (SD) and partial response (PR), respectively. Nine months after beginning the sunitinib treatment, the liver tumor size reduced to 43.0 mm with a 37% reduction, considered to be PR (Fig. 2B). The liver and kidney tumors had continuously reduced in sized compared with the baseline size of the tumors following sunitinib treatment, although the liver tumors were slightly increasing. Forty-three months after beginning the sunitinib treatment, several cerebellar metastatic lesions occurred with concurrent symptoms of headache. The main tumor of the cerebellum (25 mm of hemangioblastoma) was resected, and gamma radiation therapy (total 20 Gy, 4 Gy x5) was additionally performed against the other three small residual metastases (up to 5 mm). Fifty-

Figure 2. CT imaging of the liver tumors and a renal tumor (A) before and (B) 9 and (C) 57 months after beginning sunitinib treatment. The two left panels show multiple liver tumors and the right panel shows a renal tumor. The target lesions that were used for the response evaluation are indicated by yellow arrows.
seven months after beginning the sunitinib treatment, the treatment was stopped because of the increased size of the liver tumors (80.7 mm with a 19% increase compared with the baseline size of the tumors before beginning the sunitinib treatment, Fig. 2C). However, the kidney tumors had retained PR. In total, the patient successfully received sunitinib treatment for approximately 5 years, with maintenance of PR and SD for the liver tumors and PR for the renal tumors.

For a third-line therapy, we had two options: axitinib, another tyrosine kinase inhibitor targeting VEGFR-1, VEGFR-2, and VEGFR-3, and everolimus (15), an mTOR inhibitor. We chose axitinib treatment due to the following reasons. First, we speculated that axitinib, whose targets overlapped those of sunitinib, might also be effective in both RCC and pancreatic neuroendocrine tumors in this patient that had long been sensitive to sunitinib treatment. Second, a phase III trial showed that axitinib exerts better efficacy as a second-line treatment than sorafenib for patients with RCC, including those who have previously received sunitinib treatment (5), establishing axitinib efficacy as a second-line treatment even after sunitinib failure. However, one month after beginning axitinib treatment, it was stopped because of the progression of liver metastases. One week after treatment with everolimus was initiated as a fourth-line therapy, the patient complained of dyspnea and was diagnosed as having severe respiratory failure. He was subsequently diagnosed as having pneumocystis pneumonia with a marked elevation of KL-6 and ß-D-glucan in his blood. Despite intensive treatment with corticosteroids and antibiotic agents, he died from pneumocystis pneumonia, 27 days after the suspension of everolimus treatment.

Discussion

In recent years, new molecular-targeted drugs have been introduced into clinical use for the treatment of patients with RCC. Sunitinib, an oral multi-kinase inhibitor that targets VEGFR, platelet-derived growth factor receptors (PDGFR), KIT, and FLT3 (16), is currently used for the treatment of recurrent or unresectable RCC, as well as other VEGFR-targeted drugs including axitinib, sorafenib, and pazopanib, and an anti-VEGF antibody, bevacizumab. Inhibitors against mTOR, everolimus and temsirolimus (17), have also become therapeutic options in the treatment of RCC. Similarly, sunitinib and everolimus are currently available as treatments for patients with sporadic pancreatic neuroendocrine tumors (10, 11). In the present case, the patient was able to continuously receive multiple molecular-targeted drug therapies involving sorafenib, sunitinib, axitinib, and everolimus. In our patient, treatment with sunitinib conferred long-term efficacy without severe side effects, whereas sorafenib and everolimus showed severe toxicities resulting in the discontinuation of the therapies, and axitinib, used after sunitinib, demonstrated no efficacy.

Several recent data from pilot or small retrospective studies have suggested the promising efficacy of sunitinib for patients with VHL disease. A phase II trial by Jonasch et al. showed that among 15 patients with VHL disease who were treated with sunitinib, including a total of 20 RCCs and 20 hemangioblastomas, PR was obtained in 33% of RCC and in 0% of hemangioblastoma, and disease control (PR + SD) was observed in 90% of RCC and in 91% of hemangioblastoma cases (18). Kim et al. reported that all four patients with VHL disease-associated metastatic RCC treated with sunitinib exhibited PR with a treatment duration of 19-51 months (19). More recently, Roma et al. have shown in their retrospective analysis that 9 of 14 (64%) patients with recurrent or advanced RCC who received sunitinib treatment as a first-line therapy achieved PR, with a 2-year PFS of 71% (20). These studies, despite a relatively small number of patients analyzed, suggest that sunitinib treatment is even
more effective in patients with VHL disease compared to those with sporadic RCC or pancreatic neuroendocrine tumor. The results from a phase III trial showed PR of 31% and progression-free survival (PFS) of 11 months in patients with sporadic RCC (7, 21). Moreover, another international phase III trial for sporadic pancreatic neuroendocrine tumors demonstrated a relatively lower efficacy of sunitinib, PR of 9% and PFS of 11 months (10), whereas a phase II trial for sporadic pancreatic neuroendocrine tumors conducted in Japan reported a relatively favorable efficacy of sunitinib, PR of 50%, despite the small number of patients available for the analysis (n = 12) (22). The favorable outcome of our patient with PR maintenance from sunitinib therapy for nearly 5 years against RCC and pancreatic neuroendocrine tumor is in agreement with the results from these earlier reports (18-20, 22) and suggests that sunitinib treatment is also effective in Japanese populations with VHL disease. Further prospective studies are required to elucidate whether patients with VHL disease have a better outcome from sunitinib treatment than patients with sporadic RCC or pancreatic neuroendocrine tumors.

In addition, it should be noted that clinicians must pay careful attention to relatively rare, but severe toxicities caused by treatment with molecular-targeted drugs, including everolimus. Our patient died from pneumocystis pneumonia resulting from everolimus treatment for only one week, despite the sufficient subsequent treatments of pneumocystis pneumonia. In general, VHL-associated pancreatic neuroendocrine tumors infrequently have metastatic lesions (8-13%) (23, 24), and RCC and hemangioblastoma of the central nervous system are the major causes of death in patients with VHL disease (24). Accordingly, the application of therapy using molecular-targeted drugs, which is used to prolong the survival but not to cure the disease, should be carefully considered in each patient with VHL-associated pancreatic neuroendocrine tumor. However, in our patient, liver metastases of the pancreatic neuroendocrine tumor were markedly progressing and thought to become lethal lesions within a few months. Therefore, we consider that our decision to use drug treatments including everolimus in this patient was appropriate.

In conclusion, we described a Japanese patient with VHL-associated pancreatic neuroendocrine tumor and liver metastasis, as well as RCC and hemangioblastoma of the central nervous system, who was successfully treated with sunitinib for 57 months with PR exemplifying the best therapeutic response. Our experience supports the concept that patients with VHL disease may benefit more from VEGFR-targeting drugs than those with sporadic pancreatic neuroendocrine tumor and/or RCC. However, larger prospective clinical trials are warranted to determine the efficacy of VEGF-pathway-targeting drugs or mTOR inhibitors in the treatment of patients with VHL disease.

Author’s disclosure of potential Conflicts of Interest (COI).
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