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Erlotinib therapy for central nervous system hemangioblastomatosis associated with von Hippel-Lindau disease: a case report

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Abstract

There is a need for effective systemic therapy for central nervous system (CNS) hemangioblastomas (HBs). We report a case of erlotinib therapy for CNS HBs in a patient with von Hippel-Lindau disease, in whom the HBs were associated with diffuse leptomeningeal seeding. We provide the first report of paired serum and cerebrospinal fluid (CSF) levels of erlotinib while on standard dosing. The patient exhibited neurologic and imaging signs of recurrent CNS HBs and progressive leptomeningeal metastasis following surgery, radiation, and stereotactic radiosurgery. The patient was treated with erlotinib 150 mg daily. The patient achieved a minor response to erlotinib therapy, including clinical improvement, reduction in size of two enhancing brain lesions (one of which, however, proved at autopsy to be radiation necrosis) and stabilization of leptomeningeal enhancement. In addition, the CSF white count improved. The duration of response was 9 months. The median plasma and CSF levels of erlotinib while on treatment were 1146.06 and 247.83 ng/ml, respectively (CSF 21.6% of plasma). Erlotinib may have antitumor activity in CNS HBs.

Keywords

Erlotinib; Von Hippel-Lindau syndrome; Hemangioblastoma; CNS neoplasm

Introduction

von Hippel-Lindau (VHL) disease is an autosomal dominant hereditary cancer syndrome caused by mutation of the VHL suppressor gene. VHL is associated with a variety of neoplasms, including central nervous system (CNS) hemangioblastomas (HBs). Overexpression of a variety of growth factors and their receptors, including vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), transforming growth factor-alpha (TGF-alpha) and platelet derived growth factor-beta, have been identified in HBs [1, 2]. We report a minor response to erlotinib of recurrent CNS HBs associated with leptomeningeal dissemination in a patient with VHL. We selected erlotinib because it is a selective EGFR tyrosine kinase inhibitor. We provide the first report of plasma and cerebrospinal fluid (CSF) levels of erlotinib and its active metabolite during standard dosing of erlotinib therapy.

Clinical history

The patient underwent resection of a right cerebellar HB in 1991 at age 28. She was diagnosed with VHL on the basis of a prior resection of a pheochromocytoma and a family history of VHL (five of six siblings had VHL). The HB progressed again in 1993 and 1995 and was re-resected. In 1998, symptoms of balance and vision difficulty increased, associated with left hand and foot numbness and low back pain. Enhanced neuraxis MRI showed significant regrowth of the right cerebellar HB and several new enhancing lesions consistent with HB in the medulla, brain parenchyma, and cervical cord. In addition, there was new leptomeningeal enhancement in the basal cisterns and throughout the spine. She received 24 Gy stereotactic radiosurgery (SRS) to the right medulla and 20 Gy SRS to the right cerebellum, followed by 45 Gy external beam radiation (EBRT) to the posterior fossa and complete spine with a boost totaling 54 Gy to the lumbosacral spine and of 50 Gy to the cervical spine. Her back pain improved. In May 1999, a ventriculoperitoneal shunt was placed to treat hydrocephalus.

In April 2000, she developed new right facial weakness and numbness and increased left body numbness. Enhanced MRI showed persistent enhancement in the right cerebellum, new enhancement in the right cerebellopontine angle, and a new lesion in the pons. The spinal lesions were stable. She was referred to Henry Ford Hospital. Neurologic examination revealed reduced sensation in the right face, absent right corneal reflex, abduction weakness of the right eye, right lateral gaze-evoked nystagmus, a partial right 7th nerve palsy, reduced right-sided hearing, and mild dysarthria. She was unable to tandem walk and had mild incoordination of all limbs, generalized hyperreflexia, and reduced sensation of the left limbs. MRI in December 2000 showed enlargement of the lesions in the cerebellum and pons and new nodular enhancement within the basal cisterns, prepontine cistern, bilateral cerebellopontine cisterns, right and left internal auditory canals, the basal and suprasellar cisterns, and the cerebellar and supratentorial leptomeninges. In December 2000, lumbar CSF showed 103 mg/dl glucose, 1600 mg/dl protein, 350/mm³ RBC, and 20/mm³ WBC (65% lymphocytes, 35% monocytes). Cytologic examination was negative.

Based on clinical and MRI progression, we decided to treat the patient with erlotinib (Tarceva; OSI Pharmaceuticals, Inc). The drug was made available as part of a study involving imaging with [F-18]-3'-deoxy-3'-fluorothymidine (FLT) and positron emission tomography (PET) at the Karmanos Cancer Institute. FLT imaging was performed to determine if early changes in cell proliferation were evident after the start of treatment. The patient gave written informed consent for treatment and imaging on the protocols. Erlotinib was administered at 150 mg orally daily beginning January 22, 2001.

Within 1 day of treatment, she noted improved speech, balance, and reduced numbness on the right face and left hand that continued over the next several weeks. She was examined monthly, and MRIs were obtained every 6 weeks. The neurologic examination was stable until April, when it showed improvement in dysarthria and ataxia. The brain MRI then showed a 50% reduction of enhancement in the right cerebellar lesion and 25% reduction in the pontine lesion. The remainder of the brain lesions and the spine MRI lesions remained stable. Lumbar CSF in May showed 82 mg/dl glucose, 1386 mg/dl protein, 940 mm³ RBC, 4 mm³ WBC, and negative cytologic examination. She was stable by clinical examination and MRI in August. In October 2001, her balance was worse. The MRI showed new enhancement in the cerebellar vermis, and the posterior fossa leptomeningeal enhancement was worse. Erlotinib was discontinued. The only adverse effects she experienced from erlotinib were grade 1 skin rash, dry eyes, and diarrhea.

FLT PET showed no significant change at 7 and 14 days after the start of treatment (baseline 0.87 mean standardized uptake value, 0.90, 0.90, respectively). Serum and lumbar CSF were obtained pretreatment and after 4 months of treatment with erlotinib and were stored at -70 for VEGF measurement. Serum and CSF VEGF concentrations were determined by a quantitative sandwich enzyme immunoassay technique (Quantikine R; R & D Systems, Minneapolis, MN). The pretreatment serum and CSF VEGF levels were 312 and 282.5 pg/ml, respectively. While on treatment, serum and CSF levels were 306.5 and 281.4 pg/ml, respectively. Plasma and CSF for drug levels were obtained 4 h after the ingestion of erlotinib after 4 months on treatment and stored at -20. The samples were analyzed for erlotinib and its major metabolite formed through O-demethylation, OSI-420, by use of a validated high-pressure liquid chromatography method with triple quadrupole mass spectrometric detection (MDS Pharma Services; St. Laurent, Quebec, Canada). Three samples were run on each specimen. The median plasma and CSF levels of erlotinib were 1146.06 and 247.83 ng/ml, respectively (CSF 21.6% of plasma). Median plasma and CSF levels of OSI-420 were 130.70 and 18.71 ng/ml, respectively (CSF 14.3% of plasma).

The patient was subsequently treated with subcutaneous interferon alpha-2b and then oral temozolomide for progressive disease. In December 2003, the right cerebellar lesion increased in size and was removed because of significant mass effect. Histologic examination revealed necrosis, glial proliferation, and hematoma but no tumor. In April 2004, she received 16 Gy SRS to a sacral HB, and in January 2005, she received laser treatment for a retinal HB. The patient expired in February 2005. Autopsy revealed fibrosis in the right cerebellum and diffuse brain and spine parenchymal and leptomeningeal HBs (hemangioblastomatosis).

Discussion

HBs of the sporadic type or those associated with VHL can be managed surgically if the lesion is single [3]. However, their highly vascular nature and location in regions where resection is difficult can preclude complete excision. Focal or multifocal recurrences of HBs are common in VHL patients and often necessitate additional therapy. A non-surgical treatment option for focal disease is SRS [4]. Hemangioblastomatosis (diffuse leptomeningeal metastasis of HBs), as in our patient, is a rare complication of VHL [5, 6] and may require additional therapy for tumor control.

Systemic therapies reported for treatment of HBs are predominantly anti-angiogenic agents. We treated our patient with interferon alpha-2a at progression because of a report by Niemelä et al. [7], in which interferon alpha-2a administered to four HB patients (including three with VHL) with a combined total of 15 HBs of the CNS and 3 HBs of the retina resulted in a slight decrease in size of two CNS HBs. Nine others were stable and four enlarged. Two

retinal HBs decreased slightly in size. Aiello et al. [8] reported that SU5416, a VEGF receptor-2 inhibitor, induced rapid and durable recovery of visual function in a patient with VHL and an optic nerve HB, though the tumor remained stable. Improvement in macular edema associated with a retinal HB with SU5416 was reported by Girmens et al. [9].

Another report using SU5416 documented improvement in neurologic symptoms and a stable appearance of a spinal HB for 24 months [10]. In the largest series using SU5416, Madhusudan et al. [11] treated six VHL patients with progressive CNS HBs. Two patients showed subjective and objective neurological improvement with tumor stabilization on MRI. One of the responding patients also had complete regression of a retinal HB. Thalidomide administered to one patient with a cerebellar HB associated with progressive spinal leptomeningeal seeding produced subjective clinical improvement within 1 month and mild progressive neurological improvement. The spine MRI lesions remained stable [12]. We treated our patient with temozolomide when other agents failed because it is an agent with high penetration into CSF and it shows activity in a variety of primary and metastatic tumors.

Our case is the first report of erlotinib for treatment of CNS HBs. We selected this therapy because capillary growth stimulation via EGFR is thought to contribute to tumor growth. Erlotinib is a specific, reversible, and ATP-competitive inhibitor of tumor-cell EGFR tyrosine kinase, and it inhibits the phosphorylation of EGFR and its downstream P13/Akt and MAPK signal transduction pathways, resulting in p27-mediated cell cycle arrest. Reifemberger et al. [2] demonstrated coexpression of EGFR and pre-pro-TGF- α mRNAs by Northern blotting in each of 14 CNS HBs. In an extended series of 51 cases, immunocytochemistry demonstrated that the expression of EGFR and TGF- α was restricted to the stromal cells. Böhling et al. [1] also identified that the stromal cells of HBs express abundant EGFR. Inhibiting EGFR abolishes in vivo tumor growth of VHL-defective renal cell carcinoma cells in preclinical models [13].

Similar to other reports of successful therapy targeting growth factors in HBs, our patient experienced rapid subjective improvement and mild objective clinical improvement, and the MRI did not show significant changes. The right cerebellar lesion and one brainstem lesion decreased in size, and the brain leptomeningeal lesions that had been enlarging remained stable for 6 months. In addition, the CSF WBC elevation, which we attribute to diffuse leptomeningeal dissemination, declined to normal. The persistently high CSF protein is likely indicative of a CSF block, either from the cervical spine or posterior fossa lesions. Pretreatment CSF cytology was negative and was not an accurate measure of treatment efficacy. No change in serum or CSF VEGF levels was observed in our patient. There was no change in the thymidine PET. Imaging was done 7 and 14 days after the start of treatment and may have been too early to see changes in tumor proliferation. In patients treated with cytotoxic therapy, PET changes are typically not seen until approximately 3 weeks after the start of therapy (Shields, personal communication). At resection and autopsy, the right cerebellar lesion proved to be a necrotic lesion consistent with the delayed tissue effects of SRS, a histologic finding that others have documented in specimens of HBs after SRS [14]. The mechanism for reduced enhancement of this lesion with erlotinib therapy is not known.

Since the treatment of our patient, erlotinib has been approved by the US Food and Drug Administration for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. Erlotinib is also being used to treat malignant gliomas because of aberrant EGFR signaling associated with progression of these tumors [15]. Subsequent to the treatment of our patient, studies of the CSF penetration of erlotinib have been reported. Animal data indicate that the CSF/plasma ratio of erlotinib is approximately 1% [16]. Broniscer et al. [17] identified ventricular CSF

levels of erlotinib and OSI-420 in a child with glioblastoma on a dose of 75 mg (78 mg/M²) daily to be 7% and –9%, respectively, of plasma levels. Buie et al. [18] recently reported the pharmacokinetics of erlotinib using a nonstandard (every 72 h) dosing schedule in patients with malignant gliomas. Cerebrospinal fluid concentrations in three patients sampled ranged from 1 to 3% of peak plasma concentrations. Finally, Lassman et al. [19] reported glioblastoma tissue levels of erlotinib and OSI-420 in six patients who were treated with erlotinib at 150 mg daily prior to surgery. They found steady-state tumor trough levels of 6–8% and 5–11%, respectively, of concomitant plasma concentrations. In our patient, the CSF levels of erlotinib and its active metabolite were 21.6% and 14.3%, respectively, of the plasma level.

Effective systemic therapies for disseminated HBs are needed. Our case demonstrates that erlotinib may have antitumor activity in VHL HBs. We identified high CSF levels of the parent drug and its main metabolite in the CSF, but these values should be interpreted cautiously because of the potential for higher than normal CSF levels due to altered CSF circulation and disruption of the blood to CSF barrier by leptomeningeal disease in this case.

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References

1. Böhling T, Hatva E, Kujala M, et al. Expression of growth factors and growth factor receptors in capillary hemangioblastoma. *J Neuropathol Exp Neurol*. 1996; 55:522–527. [PubMed: 8627342]
2. Reifenberger G, Reifenberger J, Bilzer T, Wolfgang W, Collins VP. Coexpression of transforming growth factor- α and epidermal growth factor receptor in capillary hemangioblastomas of the central nervous system. *Am J Pathol*. 1995; 147:245–250. [PubMed: 7639324]
3. Jagannathan J, Lonser RR, Smith R, DeVroom HL, Oldfield EH. Surgical management of cerebellar hemangioblastomas in patients with von Hippel-Lindau disease. *J Neurosurg*. 2008; 108:210–222. [PubMed: 18240914]
4. Kano H, Niranjana A, Mongia S, et al. The role of stereotactic radiosurgery for intracranial hemangioblastomas. *Neurosurgery*. 2008; 63:443–451. [PubMed: 18812955]
5. Bakshi R, Mechtler LL, Patel MJ, et al. Spinal leptomeningeal hemangioblastomatosis in von Hippel-Lindau disease: magnetic resonance and pathological findings. *J Neuroimaging*. 1997; 7:242–244. [PubMed: 9344008]
6. Reyns N, Assaker R, Louis E, Lejeune J-P. Leptomeningeal hemangioblastomatosis in a case of von Hippel-Lindau disease: case report. *Neurosurgery*. 2003; 52:1212–1216. [PubMed: 12699568]
7. Niemelä M, Mäenpää H, Salven P, et al. Interferon α -2a therapy in 18 hemangioblastomas. *Clin Cancer Res*. 2001; 7:510–516. [PubMed: 11297241]
8. Aiello LP, George DJ, Cahill MT, et al. Rapid and durable recovery of visual function in a patient with von Hippel-Lindau syndrome after systemic therapy with vascular endothelial growth factor receptor inhibitor SU5416. *Ophthalmology*. 2002; 109:1745–1751. [PubMed: 12208726]
9. Girmens J-F, Erginay A, Massin P, et al. Treatment of von Hippel-Lindau retinal hemangioblastoma by the vascular endothelial growth factor receptor inhibitor SU5416 is more effective for associated macular edema than for hemangioblastomas. *Am J Ophthalmol*. 2003; 136:194–196. [PubMed: 12834696]
10. Schuch G, de Wit M, Höltje J, et al. Hemangioblastomas: diagnosis of von Hippel-Lindau disease and antiangiogenic treatment with SU5416. *J Clin Oncol*. 2005; 23:3624–3626. [PubMed: 15908674]
11. Madhusudan S, Deplanque G, Braybrooke JP, et al. Anti-angiogenic therapy for von Hippel-Lindau disease (research letter). *JAMA*. 2004; 291:943–944. [PubMed: 14982909]

12. Piribauer M, Dieckmann K, Birner P, et al. Stabilization of a progressive hemangioblastoma under treatment with thalidomide. *J Neurooncol.* 2004; 66:295–299. [PubMed: 15015660]
13. Smith K, Gunaratnam L, Morley M, et al. Silencing of epidermal growth factor receptor suppresses hypoxia-inducible factor-2-driven VHL^{-/-} renal cancer. *Cancer Res.* 2005; 65:5221–5230. [PubMed: 15958567]
14. Park YS, Chang JH, Chang JW, Chung SS, Park YG. Gamma knife surgery for multiple hemangioblastomas. *J Neurosurg.* 2005; 102:97–101. [PubMed: 15662788]
15. Haas-Kogan DA, Prados MD, Tihan T, et al. Epidermal growth factor receptor, protein kinase B/ Akt, and glioma response to erlotinib. *J Natl Cancer Inst.* 2005; 97:880–887. [PubMed: 15956649]
16. Vogelbaum MA, Nelms JL, Daneshvar H, Cutter CT, Gill S. Evaluation of tissue penetration of Tarceva [OSI-774] in a rat xenograft brain tumor model (abstract). AACR-NCI-EORTC Symposium on Targeted Therapeutics. 2003
17. Broniscer A, Panetta JC, O'Shaughnessy M, et al. Plasma and cerebrospinal fluid pharmacokinetics of erlotinib and its active metabolite OSI-420. *Clin Cancer Res.* 2007; 13:1511–1515. [PubMed: 17332296]
18. Buie LW, Lindley C, Shih T, et al. Plasma pharmacokinetics and cerebrospinal fluid concentrations of erlotinib in high-grade gliomas: a novel, phase 1, dose escalation study (abstract). *Proc ASCO.* 2007; 25:88.
19. Lassman AB, Rossi MR, Raizer JJ, et al. Molecular study of malignant gliomas treated with epidermal growth factor receptor inhibitors: tissue analysis from North American Brain Tumor Consortium Trials 01–03 and 00–01. *Clin Cancer Res.* 2005; 11:7841–7850. [PubMed: 16278407]