Rationale and Evidence for Sunitinib in the Treatment of Malignant Paraganglioma/Pheochromocytoma

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Context: Paragangliomas are tumors that develop from extraadrenal chromaffin cells. Approximately 20% of paragangliomas are malignant, and surgical resection is considered the primary treatment when possible. The optimal systemic treatment for advanced disease is undefined, due in part to lack of effective agents. Here we report our experience suggesting that sunitinib is an effective agent in this malignancy.

Setting and Patients: Three patients with metastatic paraganglioma were treated with sunitinib at the Princess Margaret Hospital. Limited analyses of tumor tissue and germline DNA were available.

Intervention: Sunitinib at a standard dose (50 mg daily, 4 wk on, 2 wk off) was titrated to patient tolerance.

Results: One patient has achieved a near complete response, and two patients demonstrated partial responses. Two patients demonstrated germline defects suggesting a pseudo-hypoxic drive to the tumor whereas the third demonstrated immunohistochemical evidence of this phenomenon.

Conclusions: Sunitinib appears to be an active agent in this malignancy based on this limited cohort, with an understandable mechanism of action similar to that described in other hypoxia-driven tumors. A single arm phase 2 trial is underway. **(*J Clin Endocrinol Metab* 94: 5–9, 2009)**

Paragangliomas are tumors that develop from extraadrenal chromaffin cells. Approximately 20% of paragangliomas are malignant, and surgical resection is considered the primary treatment when possible. The optimal systemic treatment for advanced disease is undefined, due in part to lack of effective agents. Here we report three cases demonstrating an impressive clinical response to treatment with the tyrosine kinase inhibitor sunitinib. We discuss the molecular basis for such a response and demonstrate that such a mechanism may be active in our cohort. Sunitinib thus appears to be a promising treatment for metastatic paragangliomas, and a single arm phase 2 trial is currently underway.

Case Report 1

A previously well 55-yr-old Caucasian man presented with a 2-month history of right flank discomfort. An ultrasound scan revealed a right kidney mass, and computed tomography (CT) confirmed a large vascular right renal mass extending into the retroperitoneum. Magnetic resonance imaging delineated a 16-cm exophytic mass centered on the right renal pelvis causing displacement and dilation of the right renal collecting system. It invaded the inferior vena cava and the renovascular structures and was intimately associated with the duodenum. Both bone scintigraphy and CT of the thorax were unremarkable. He had no endocrine symptoms suggestive of catecholamine excess. There was no family history of features suggesting multiple endocrine neoplasia including pheochromocytoma or paraganglioma.

A core biopsy containing limited tumor material was diagnosed as carcinoma with high-grade elements. Cells with clear cytoplasm were seen. There was focally positive pan-cytokeratin staining, and cytokeratin-7 staining was negative. Although not definitive, the features at biopsy were consistent with renal cell carcinoma (RCC).

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Abbreviations: CT, Computed tomography; HIFα, hypoxia-inducible factor-α; RCC, renal cell carcinoma; SDHB, succinate dehydrogenase subunit B; VEGFR, vascular endothelial growth factor receptor; VHL, von Hippel-Lindau.

After multidisciplinary review, he commenced sunitinib treatment at a standard schedule (50 mg daily for 4 wk on, 2 wk off) with a plan to reassess resectability if some response to systemic therapy was observed. He experienced mild but manageable toxicities of grade 3 neutropenia (requiring two treatment delays), grade 2 plantar-palmar erythema, and fatigue as well as grade 1 hypertension requiring treatment with an angiotensin converting enzyme inhibitor.

After two cycles of treatment, he was symptomatically improved with resolved flank pain, and the mass had diminished in size on both physical and CT examination. After six cycles of sunitinib therapy, the mass measured 9.4 cm on CT compared with baseline of 14.3 cm, meeting Response Evaluation Criteria in Solid Tumors (RECIST) criteria for a partial radiological tumor response (Fig. 1A). His sunitinib was stopped 3 wk before surgery.

He underwent an open right radical nephrectomy and lymphadectomy with resection of the mass, which was found to invade into the retrocaval and aortocaval areas.

Histological examination revealed a paraganglioma (Fig. 2A; see Table 1). Succinate dehydrogenase subunit B (SDHB) gene mutational analyses demonstrated a previously described missense germline mutation in exon 4 (I127S) in peripheral blood leukocytes; the von Hippel-Lindau (VHL) gene sequence was wild type. Postoperatively, he restarted sunitinib (after a break of 8 wk in total), but after two cycles at a dose reduction of 37.5 mg (4 wk on, 2 wk off), there was clear CT evidence of progression, with relapse in a lymph node mass posterior to the uncinate process of the pancreas (CT not shown). He remains in good health and has recently progressed after three cycles of CVD (cyclophosphamide, vincristine, and dacarbazine) chemotherapy.

Case Report 2

A 28-yr-old previously well male was referred for assessment after partial cystectomy for a 7-cm paraganglioma of the urinary bladder 1 month previously. Four years earlier, he presented with intermittent hematuria that ultimately led to a diagnostic cystoscopy 2 months before the current presentation. There was no family history to suggest features of multiple endocrine neoplasia, VHL, or neurofibromatosis. Preoperative staging including CT and Metaiodobenzylguanidine scans were unremarkable. However, 24-h urinary metanephrines were elevated at four times the upper limit of normal.

Surgical pathology revealed a paraganglioma invading the muscularis propria and perivesicular fat with frequent mitoses and four involved lymph nodes. Given his advanced stage, he was treated adjuvantly with combined radiation and cisplatin followed by four courses of cisplatin and etoposide.

He was subsequently lost to follow-up for 1 yr after which he presented with widespread metastatic disease in multiple organs including T3 spinal cord compression. He was managed with decompressive laminectomy and metastasectomy followed by adjuvant radiation to the area. Subsequently, he was started on sunitinib, and after two cycles a significant partial RECIST response was documented in lungs and pelvic lymph nodes. He continues on treatment and has now achieved a near complete response on CT scan after six cycles (Fig. 1B). DNA sequencing revealed a previously undescribed germline mutation in SDHB exon 6 (C189F). He has now completed 40 wk treatment, and his disease remains stable.

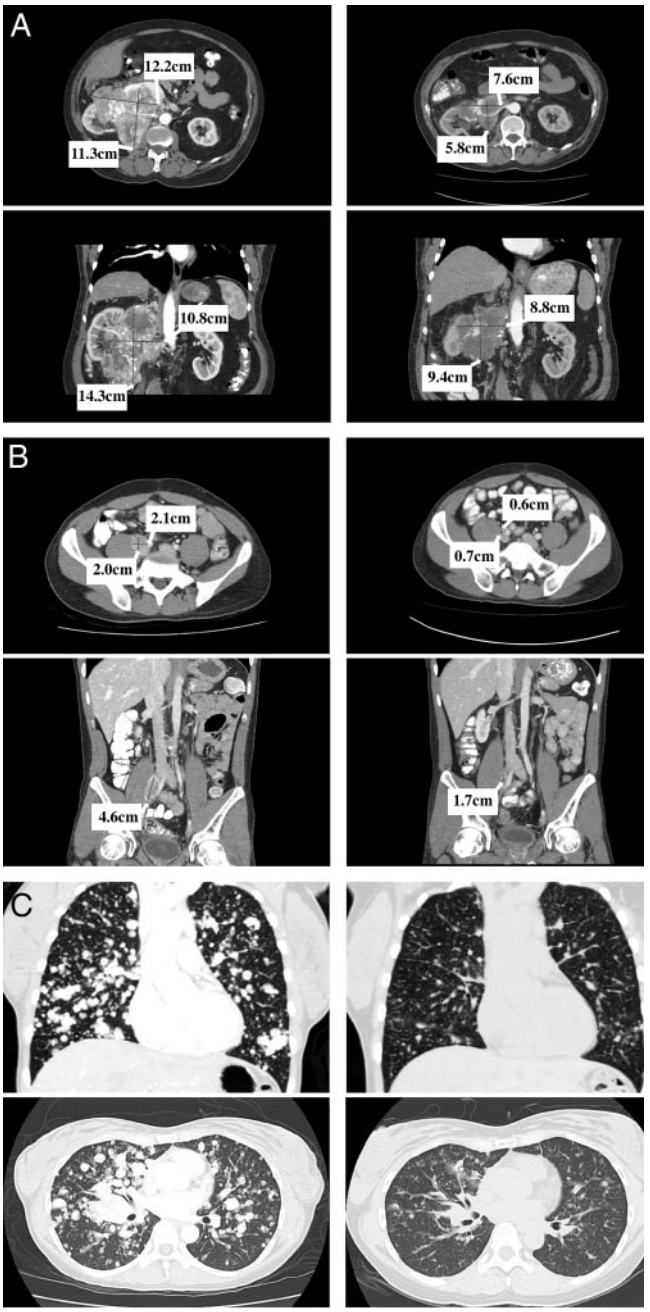

FIG. 1. A, CT scans documenting responses to sunitinib in patient 1. Pretreatment scan (*left*) demonstrating right renal pelvis mass in corneal (11.3 × 12.2 cm) and sagittal (10.8 × 14.3 cm) sections with post-treatment scans (*right*) demonstrating a significant reduction in size (5.8 cm × 7.6 cm and 8.8 cm × 9.4 cm respectively). B, CT scans documenting response to sunitinib in patient 2. Pretreatment scan (*left*) demonstrating right pelvic lymph node in coronal (2.1 × 2 cm) and sagittal (4.6 cm) sections with post-treatment scans (*right*) demonstrating a significant reduction in size (0.7 × 0.6 cm and 1.7 cm respectively). C, Coronal and sagittal views of lung fields of patient 3 demonstrating a significant reduction in lung metastases.

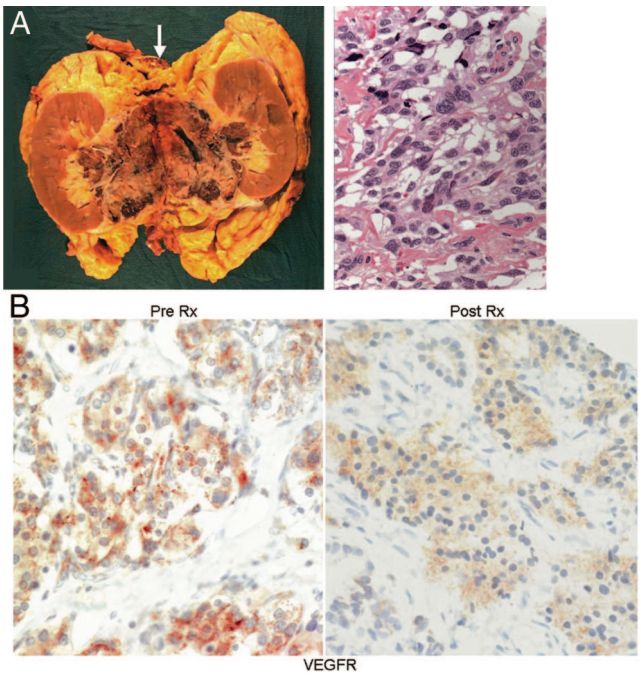

FIG. 2. Pathological correlates from the cases discussed. A, Paraganglioma, gross and histological specimen from case report 1; B, reduction in VEGFR staining demonstrated after treatment with sunitinib in case report 3.

Case Report 3

A 41-yr-old multiparous female presented with abdominal pain and a left flank mass. MIBG imaging revealed abnormal uptake consistent with an isolated CT-demonstrated left 15-cm suprarenal mass. Tumor markers confirmed a 33-fold elevation in 24-h urinary metanephrine excretion. The mass was resected, and histology confirmed a paraganglioma with metastatic involvement of a periaortic lymph node. Blood DNA sequencing did not reveal any abnormalities in SDHB, SDHD, RET, or VHL genes.

She remained in biochemical remission for 1 yr after which urinary catecholamines started to progressively rise. CT and octreoscanning suggested disease recurrence in the chest involving both lung fields. Treatment with a somatostatin analog for 6 months was ineffective. Similarly, 3 months of a phase 1 trial of a focal kinase adhesion inhibitor was ineffective. Subsequently, treatment with three cycles of sunitinib resulted in a marked (90%) reduction in urinary metanephrines and measurable regression of the bilateral pulmonary metastases. Adverse reactions included hypertension controlled with the α-blocker prazosin and a self-limited facial skin rash. Posttreatment biopsy revealed down-regulation of vascular endothelial growth factor receptor (VEGFR) expression (Fig. 2B). She remains on treatment with disease that continues to regress after 40 wk (Fig. 1C).

Discussion

Pheochromocytomas and paragangliomas are tumors of neural crest-derived paraganglia that exist throughout the body in the distribution of the sympathetic and parasympathetic nervous system. The current World Health Organization classification (1) reserves the term pheochromocytoma for intraadrenal tumors, whereas tumors arising in extraadrenal paraganglia are classified as paragangliomas. These tumors can either be sporadic or occur in the context of hereditary cancer syndromes such as VHL disease, multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1, or germline SDHB, SDHC, or SDHD (2–5).

Established treatment modalities for malignant paraganglioma include surgery and radionucleotide treatment. Systemic treatment approaches advocated to date for these patients have included combination chemotherapy with CVD (cyclophosphamide, vincrsitine, dacarbazine) (6, 7), MAID (mesna, doxorubicin, dacarbazine, ifosfamide) (8), gemcitabine (9), paclitaxel (10), and etoposide-cisplatin (11); however, treatment experience with all these regimens is limited and toxicities severe. There are no reports of targeted therapies for this malignancy. More experience with targeted agents is available for the treatment of neuroendocrine tumors in general (12) where targeted regimens based on angiogenesis have modest effectiveness (13–16).

Sunitinib is an oral multitargeted receptor tyrosine kinase inhibitor with antiangiogenic and antitumor activity, which targets platelet-derived growth factor receptor (PDGFR), VEGFR, KIT, and FLT3. In malignancies such as RCC where a therapeutic role of sunitinib has been established, the absence of the *VHL* gene causes accumulation of hypoxia-inducible factor-α (HIFα) and the production of several growth factors, including VEGF and platelet-derived growth factor (PDGF) against which sunitinib has efficacy (17).

Recent insights into the genetics of hereditary paraganglioma syndromes suggest a plausible mechanism of action of sunitinib in this malignancy. Tumors from patients with germline mutations of VHL, SDHB, SDHC, or SDHD as well as selected sporadic tumors demonstrate evidence of HIF dysregulation and activation of hypoxia-inducible target genes (18, 19). A major function of the VHL tumor suppressor protein is the targeting of the α-subunits of the HIF-1 and HIF-2 transcription factors for ubiquitination and degradation (20). The ability of VHL to bind to the HIFα subunits depends on the hydroxylation of two proline residues (21). Hydroxylation of these residues by proyl hydroxylases is dependent on the availability of oxygen. Furthermore, inactivation of succinate dehydrogenases increases intracellular succinate, which impairs HIF proyl hydroxylases, leading to HIF dysregulation (22). This pseudohypoxic drive is functionally analogous to defects in the VHL protein and may account for the activity of sunitinib seen in our patients with paragangliomas (Fig. 3). Our second patient demonstrates a previously undescribed mutation in a critical iron-sulfur binding site that *in silico* analysis (23) suggests is likely to be damaging. Several mutations have been reported near this locus that have similarly resulted in malignant phenotypes (24). Although our third patient had normal germline analysis of SDHB, SDHD, and VHL, we demonstrated immunohistochemical findings suggestive of down-regulation of VEGFR on rebiopsy (Fig. 2B), the mechanism of which remains unclear but which is consistent with the clinical response of the tumor.

To our knowledge, these are the first reports of malignant paragangliomas responding to treatment with sunitinib (Table 1). Of particular concern with the use of this agent in this condition, is the po-

TABLE 1. Characteristics of patients described in this report

Patient	Histology	Previous systemic treatments	Molecular results	Course on sunitinb including toxicities	Duration of response on sunitinib (wk)
1	Metastatic paraganglioma, involving 1/1 lymph node, 10% Ki67 index. chromogranin, S100, tyrosine hydroxylase positive	None	SDHB exon 4 (I127S)	Neutropenia, rash, hypertension	24[a]
2	Metastatic paraganglioma involving 4/4 lymph nodes, chromogranin, synaptophysin positive, Ki67 index 5–10%	Chemotherapy (cisplatin ± etoposide) + radiation to pelvis	SDHB exon 6 (C189F)	Mild anorexia, diarrhea, hypothyroidism	40 (ongoing)
3	Metastatic paraganglioma, 1/25 nodes positive, synaptophysin, chromogranin, tyrosine hydroxylase positive, Ki67 index 20%	Sandostatin, FAK inhibitor	No mutation in SDHB, -C, and -D or RET	Hypertension[b]	40 (ongoing)

All patients started at the standard dose of 50 mg (4 wk on, 2 wk off). FAK, Focal adhesion kinase.

[a] Patient 1 required an 8-wk break in the perioperative period before restarting at a lower dose that proved ineffective.

[b] Required treatment with prazosin 5 mg for control of hypertension (Labetalol and Amoldipine relatively ineffective).

tential for an exacerbation of hypertension, a side effect well characterized with tyrosine kinase inhibitors of VEGF (25, 26). Thus, control of baseline hypertension is of critical importance. The treating clinician must also be attentive to other side effects such as hypothyroidism, neutropenia, thrombocytopenia, diarrhea, and left ventricular dysfunction in the ongoing management of these patients (27).

Given these results reported, further investigation of sunitinib in paraganglioma is warranted, and a single arm phase 2 trial is underway. This trial will aim to evaluate the clinical benefit rate [complete response (CB) + partial response (PR) + stable disease (SD)] of sunitinib in metastatic paraganglioma/ pheochromocytoma. Secondary endpoints include the effect of sunitinib on biochemical markers of disease, overall survival, time to progression, overall response rate (PR + CR), and toxicity. There will initially be up to 28 patients enrolled in a two-stage Fleming design. This information will provide crucial information about the tolerability, duration of treatment, risks, and benefits of sunitinib in this condition. The mechanism of action suggested

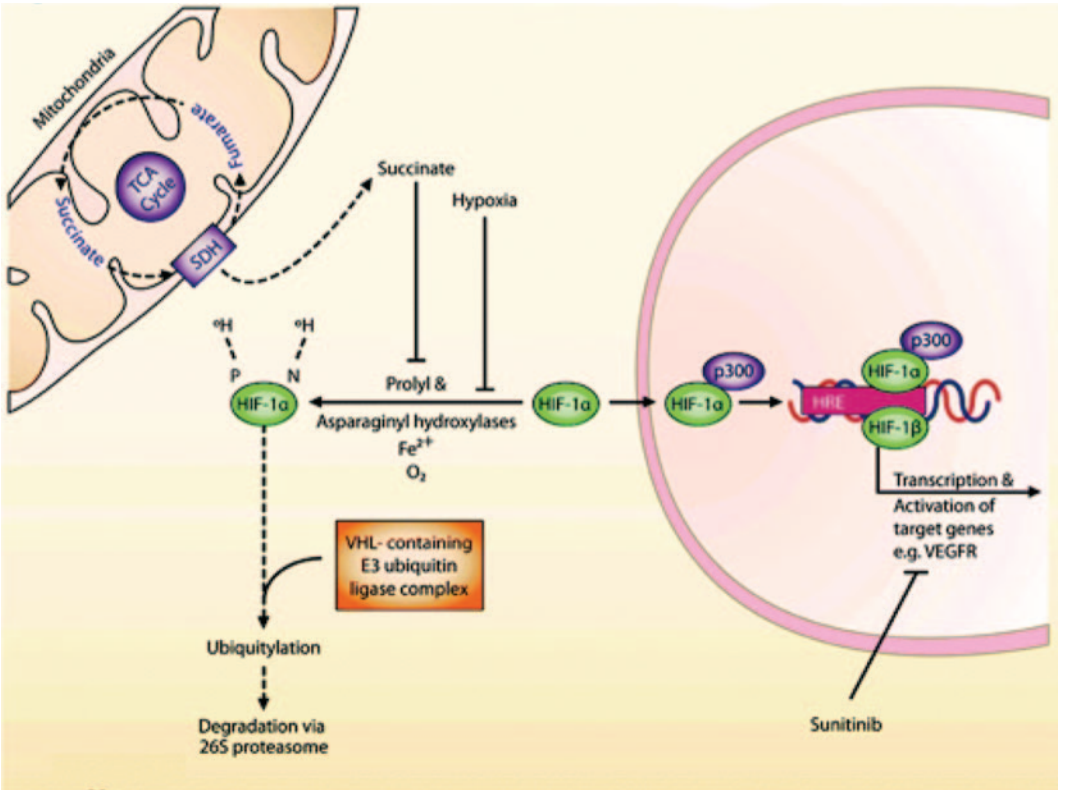

FIG. 3. Schematic demonstrating the pathways suggested to underlie the sensitivity of paragangliomas and the pseudohypoxic drive to sunitinib acting through relevant tyrosine kinases.

with sunitinib suggests that other drugs of benefit in HIF-driven RCC such as sorafenib, bevacizumab, and temsirolimus may also have activity in this setting.

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