CASE REPORT

Sunitinib treatment for refractory malignant pheochromocytoma

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Abstract

We report the clinical response and adverse events of a female patient treated for recurrent malignant pheochromocytoma using the tyrosine kinase inhibitor sunitinib. A 41-year-old woman underwent adrenectomy and nephrectomy forpotentially malignant adrenal pheochromocytoma. Fifty-four months after surgery, abdominal computed tomography (CT) and Iodine-131 metaiodobenzylguanidine(^{131}I-MIBG) scintigraphy revealed multiple tumors in the liver. Two chemotherapy protocols were administered in succession (first line: cyclophosphamide/vinblastine/dacarbazine; second line: cisplatin/docetaxel/ifomide). Despite these treatments, however, the tumors continued to progress. Treatment with sunitinib was initiated, but the patient quickly developed critical hypertension caused by tumor lysis syndrome. The sunitinib dose was reduced, and a partial response, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), was observed after 6 treatment cycles. Moreover, no severe adverse events occurred during this lower-dose sunitinib treatment. Unfortunately, sunitinib treatment became unaffordable for the patient, who eventually resorted to palliative care and died 37 months later. This case study is consistent with previous reports indicating that appropriate doses of sunitinib can induce a partial antitumor response in patients with refractory pheochromocytoma.

Abbreviations:

CT	- computed tomography
^{131}I-MIBG	- Iodine-131 metaiodobenzylguanidine
CVD	- cyclophosphamide /vinblastine/dacarbazine
TLS	- tumor lysis syndrome
PR	- partial response
RECIST	- Response Evaluation Criteria in Solid Tumor
VEGF	- vascular endothelial growth factor
HIF	- hypoxia-inducible factor
SDH	- succinate dehydrogenase

INTRODUCTION

Neuroendocrine tumors can arise in almost every organ of the body and represent a variety of clinical manifestations. Pheochromocytoma is a rare catecholamine-secreting neuroendocrine tumor that arises from chromaffin tissue within the adrenal medulla and at extra-adrenal sites.

The incidence of recurrent pheochromocytoma ranges from 3% to 36%, and common sites of recurrence include the lymph nodes, bones, liver, and lungs (Chrisoulidou *et al.* 2007, Pacak *et al.* 2007; Adjalle *et al.* 2009). Malignant pheochromocytoma cannot be diagnosed histologically; rather, it is most often identified after metastasis to other organs. Moreover, no standardized treatment for malignant pheochromocytoma has been established, and the prognosis remains poor. Average time to recurrence after initial surgery is approximately 4–8 years, but recurrence after 10 years or more is also common (Tanaka *et al.* 1993; Harari & Inabnet 2011; Morikawa *et al.* 2001; Park *et al.* 2011). Therefore, long-term follow-up examinations, including computed tomography (CT) scanning and other blood and urinary tests, are critical for early detection.

We treated a case of recurrent pheochromocytoma 54 months after initial surgery. The 41-year-old patient demonstrated chemoresistance to two standard antitumor regimes and was then treated with the tyrosine kinase inhibitor sunitinib. While sunitinib exhibited an excellent antitumor effect, the patient showed severe adverse events, including critical hypertension due to tumor lysis. The unique clinical course and adverse events during sunitinib therapy are documented in this report.

CASE REPORT

A 41-year-old woman was referred to our hospital with complaints of palpitation and headache. On initial examination, systolic/diastolic blood pressure was 200/110 mmHg, indicating severe hypertension. Fractionation revealed elevated blood levels of all three catecholamines (epinephrine, norepinephrine, and dopamine). Abdominal CT revealed a 10-cm tumor in the right adrenal gland. Iodine-131 metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy showed abnormal ^{131}I-MIBG accumulation at the tumor site. A diagnosis of adrenal pheochromocytoma was made on the basis of these findings. Her hypertension was first brought under control by administration of the α-blocker doxazosin mesylate (12 mg). Combined right adrenectomy–nephrectomy was performed. Pathological examination of the specimen revealed adrenal pheochromocytoma with both high mitotic count and MIB-1 labeling index, indicating severe malignant potential. Thereafter, the patient was closely monitored at an outpatient clinic by blood examinations, CT, and ^{131}I-MIBG scintigraphy.

A follow-up CT performed 54 months after surgery revealed multiple liver tumors (Figure 1a) and ^{131}I-MIBG scintigraphy showed abnormal accumulations at the same sites. No other organs were involved. The patient was diagnosed with recurrent pheochromocytoma, and CVD (cyclophosphamide/vinblastine/dacarbazine) combination chemotherapy was initiated according to the following protocol: 800 mg/body surface area (m^2) cyclophosphamide on day one, 1.7 mg/m^2 vincristine on day one, and 700 mg/m^2 dacarbazine on day two. This protocol was repeated once every 28 days. After 4 cycles of CVD therapy, however, liver metastasis continued as revealed by abdominal CT. A second-line chemotherapy (cisplatin/docetaxel/ifomide) was administered according to the following protocol: 70 mg/m^2 cisplatin on day one, 70 mg/m^2 docetaxel on day one, and 1000 mg/m^2 ifomide on days one, two, and three. Two cycles of second-line chemotherapy were administered, but the disease continued to progress (Figure 1b).

Sunitinib is an inhibitor of multiple tyrosine kinases and is approved for the treatment of renal cell carcinoma. It is not approved for the treatment of malignant pheochromocytoma, although two previous studies reported excellent antitumor efficacy (Table 1). The

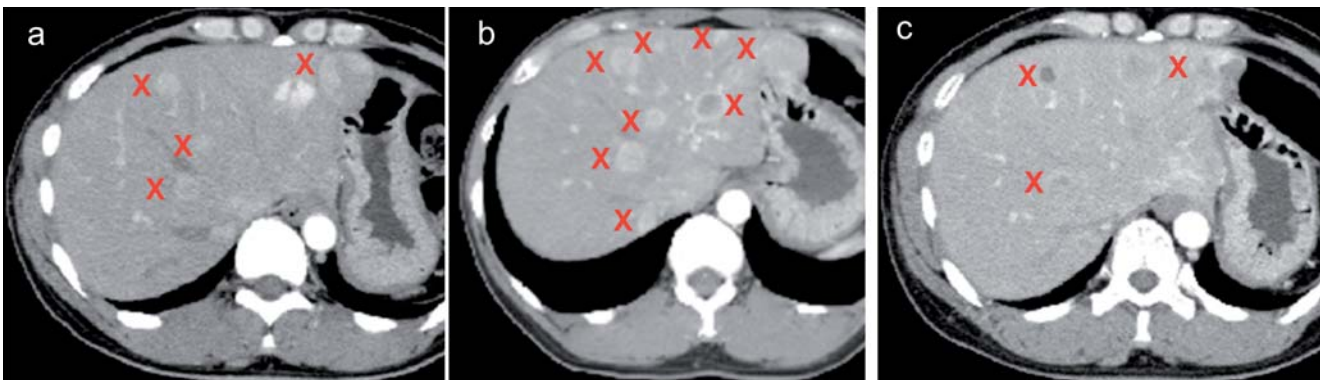

Fig. 1. Abdominal computed tomography showing recurrent disease in the liver. (a) pretreatment, (b) after chemotherapy, (c) after sunitinib treatment. **X**: tumor occupied region.

Tab. 1. Case studies of sunitinib treatment for malignant pheochromocytoma.

	Age (y)	Gender	hereditary	Previous treatment	Dose (mg)	Critical HT with TLS	RECIST response	Duration of response (months)
Jimenez *et al.*	32	F	hereditary	surgery	NA	present	PR	NA
Park *et al.*	17	M	sporadic	surgery chemo	25–37.5	absent	PR	1
Zukauskaite *et al.*	54	F	sporadic	surgery chemo	12.5–50	present	SD	10
Our case	41	F	sporadic	surgery chemo	25–50	present	PR	9

F: female, M: male, chemo: chemotherapy, NA: not available, HT: hypertension, TLS: tumor lysis syndrome, PR: partial response, RECIST: Response Evaluation Criteria in Solid Tumors

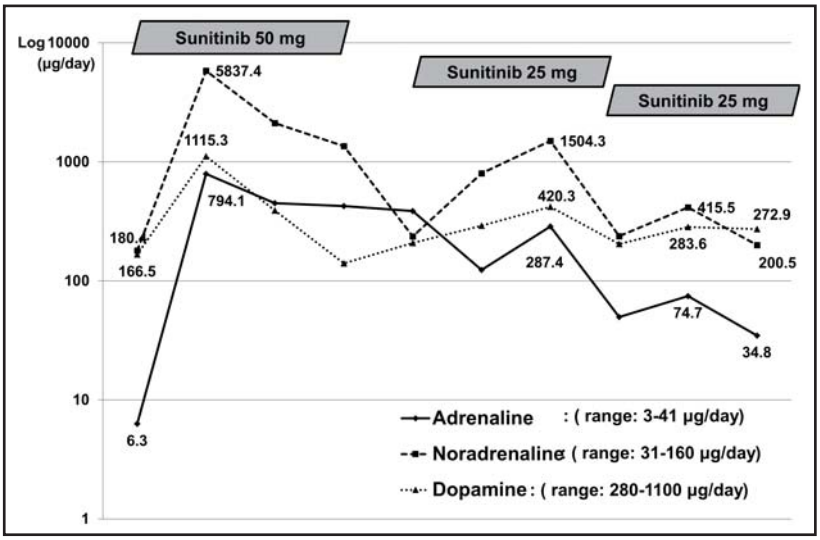

Fig. 2. Modulation of urinary catecholammines by sunitinib treatment.

Institutional Review Board of our hospital approved the use of sunitinib for our refractory patient. The patient was informed that the efficacy of sunitinib for malignant pheochromocytoma is still under investigationand she gave her consent. The cost of the initial sunitinib treatment was covered by the hospital.

Sunitinib was initiated at 50 mg/day, the common treatment dose for renal cell carcinoma. On day 5 of treatment, grade 3 nausea and general fatigue developed. Results of laboratory investigations on day 5 were as follows: lactate dehydrogenase, 1 004 U/l (normal, 120–245 U/l); uric acid, 7.1 mg/dl (normal, 2.7–7.0 mg/dl); serum creatinine, 1.62 mg/dl (normal, 0.46–0.82 mg/dl); corrected calcium, 7.7 mg/dl (normal, 8.2–10.0 mg/dl). On day 7, tachycardia and syncope occurred, and her blood pressure was 240/140 mmHg. Moreover, a 24-hour urine test revealed drastically elevated levels of all three catecholamines: epinephrine, 449.1 μg/day (normal, 3.0–41.0 μg/day); norepinephrine, 5837.4 μg/day (normal, 31–160 μg/day); dopamine, 1 115.3 μg/day (normal, 280–1 100 μg/day) (Figure 2). Tumor lysis syndrome (TLS) was suspected, and sunitinib treatment was temporarily discontinued.

For all subsequent treatment cycles, the patient received sunitinib at a reduced dose of 25 mg/day for two weeks, followed by two weeks without sunitinib before the next cycle. During the second cycle, she experienced no severe adverse events (AE). A partial response (PR) was documented after 6 cycles of this lower-dose sunitinib treatment regime according to the Response Evaluation Criteria in Solid Tumors (RECIST). This partial response persisted for 9 months (Figure 1c). Unfortunately, the patient discontinued sunitinib treatment because of the expenses involved and opted for palliative therapy that included a somatostatin analog, an angiotensin II receptor inhibitor, and a cyclooxygenase-2 inhibitor. The patient died 37 months after sunitinib treatment was discontinued.

DISCUSSION

Several clinical and molecular markers for pheochromocytoma have been proposed (Chrisoulidou *et al.* 2007; Ayala-Ramirez *et al.* 2011; Feng *et al.* 2011; Park *et al.* 2011) but no clear correlations between these markers and disease prognosis have been established. In 2002, Thompson proposed the pheochromocytoma of the adrenal gland scaled score (PASS) as a pathological predictor. The patient in this study scored 6 points on PASS, suggesting that she suffered from a highly aggressive form of pheochromocytoma. However, the

predictive efficacy of the PASS score remains contentious (Agarwal *et al.* 2010).

Many oncologists consider ^{131}I-MIBG radiation therapy the most effective treatment for recurrent pheochromocytoma (Safford *et al.* 2003; Chrisoulidou *et al.* 2007; Gedik *et al.* 2008). In Japan, however, ^{131}I-MIBG radiation therapy is not covered by health insurance and few institutions offer this treatment, so two combination chemotherapy regimens were administered instead. A standard combination chemotherapy protocol for malignant pheochromocytoma has not yet been established because only a few nonrandomized studies have been conducted (Chrisoulidou *et al.* 2007; Pacak *et al.* 2007; Adjalle *et al.* 2009; Harari & Inabnet 2011). Combination CVD therapy is one of the most widely used protocols, with biochemical and/or radiological response rates ranging from 52% to 72% (Huang *et al.* 2008; Adjelle *et al.* 2009; Nomura *et al.* 2009). However, CVD therapy does not increase survival and was not effective in our patient(Huang *et al.* 2008; Adjelle *et al.* 2009; Nomura *et al.* 2009).

Abnormal microangiogenesis has been detected in numerous malignant tumors. In malignant pheochromocytoma, high levels of vascular endothelial growth factor (VEGF) are associated with poor prognosis. Hypoxia-inducible factors (HIFs) are transcription factors that induce the expression of many genes known to support tumor microangiogenesis, including VEGF. Germline mutations in the von Hippel–Lindau tumor suppressor gene, the succinate dehydrogenase (SDH) B subunit gene, and the SDH D subunit gene can lead to malignant pheochromocytoma by inhibiting HIF degradation, causing overexpression of angiogenic factors that activate multiple tyrosine kinase pathways (Grogan *et al.* 2011; Ye *et al.* 2011). It is therefore possible that tyrosine kinase inhibitors can disrupt microangiogenesis (or other tumorigenic processes) in cases of malignant pheochromocytoma, and indeed three previous case studies reported favorable outcomes (Jimenez *et al.* 2009; Park *et al.* 2009,Zukauskaite *et al.* 2011).

Tumor lysis syndrome, caused by the rapid lysis of malignant cells with concomitant release of intracellular contents, is a serious adverse event in anticancer treatment most commonly encountered during the treatment of hematologic malignancies (Coiffier *et al.* 2008; Mughal *et al.* 2010). In particular, 17–47% of patients with Burkitt's lymphoma, acute lymphoblastic lymphoma, or acute myeloid leukemia develop TLS (Coiffier *et al.* 2008). In contrast, the rate of TLS in patients with solid tumors is only 3% (Gemici 2006; Coiffier *et al.* 2008; Maghal *et al.* 2010). However, Gemici (2006) concluded that TLS in cases of solid tumors was associated with higher mortality than TLS in cases of hematologic malignancies. Recently, TLS caused by molecular target drugs was reported (Nicholaou *et al.* 2007; Saylor & Reid 2007; Joshita *et al.* 2010; Michels *et al.* 2010), including critical hypertension in a patient treated with sunitinib (Jimenez *et al.* 2009). We suggest that critical hypertension is a potential adverse event of tyrosine kinase inhibitors, particularly when used for the treatment of malignant pheochromocytoma.

A World Health Organization classification of neuroendocrine tumors, including pheochromocytoma in the digestive system, was proposed in 2010 using only the Ki-67 index and mitotic count (Kloppel 2011; Oberg & Castellano 2011). The results presented here will aid in establishing standard therapeutic strategies and postoperative care regimes for cases of malignant pheochromocytoma or other rare neuroendocrine tumors. Although several reports now indicate that tyrosine kinase inhibitors have therapeutic potential in cases of malignant pheochromocytoma (Jimenez *et al.* 2009; Park *et al.* 2009, Zukauskaite *et al.* 2011), an international collaborative trial is necessary to confirm these results and to study the efficacy of this class of drugs on other rare malignancies.

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REFERENCES

1 Adjalle R, Plouin PF, Pacak K, Lehnert H (2009). Treatment of malignant pheochromocytoma. Horm Metab Res. **41**: 687–696.
2 Agarwal A, Mehrotra PK, Jain M, Gupta SK, Mishra A, Chand G, et al (2010). Size of the tumor and pheochromocytoma of the adrenal gland scaled score (PASS): can they predict malignancy? World J Surg. **34**: 3022–3028.
3 Ayala-Ramirez M, Feng L, Johnson MM, Ejaz S, Habra MA, Rich T, et al (2011). Clinical risk factors for malignancy and overall survival in patients with pheochromocytomas and sympathetic paragangliomas: primary tumor size and primary tumor location as prognostic indicators. J Clin Endocrinol and Metab. **96**: 717–725.
4 Chrisoulidou A, Kaltsas G, Ilias I, Grossman AB (2007). The diagnosis and management of malignant phaeochromocytoma and paraganglioma. Endocr-Relat Cancer **14**: 569–585.
5 Coiffier B, Altman A, Pui CH, Younes A, Cairo MS (2008). Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. **26**: 2767–2778.
6 Feng F, Zhu Y, Wang X, Wu Y, Zhou W, Jin X, et al (2011). Predictive factors for malignant pheochromocytoma: analysis of 136 patients. J Urol. **185**: 1583–1590.
7 Gedik GK, Hoefnagel CA, Bais E, Olmos RA (2008). 131I-MIBG therapy in metastatic phaeochromocytoma and paraganglioma. Eur J Nucl Med Mol Imaging **35**: 725–733.
8 Gemici C (2006). Tumour lysis syndrome in solid tumours. Clin Oncol (R Coll Radiol) **18**: 773–780.
9 Grogan RH, Mitmaker EJ, Duh QY (2011). Changing paradigms in the treatment of malignant pheochromocytoma. Cancer Control **18**: 104–112.
10 Harari A, Inabnet WB, 3rd (2011). Malignant pheochromocytoma: a review. Am J Surg. **201**: 700–708.
11 Huang H, Abraham J, Hung E, Averbuch S, Merino M, Steinberg SM, et al (2008). Treatment of malignant pheochromocytoma/paraganglioma with cyclophosphamide, vincristine, and dacarbazine: recommendation from a 22-year follow-up of 18 patients. Cancer **113**: 2020–2028.

12 Jimenez C, Cabanillas ME, Santarpia L, Jonasch E, Kyle KL, Lano EA, et al (2009). Use of the tyrosine kinase inhibitor sunitinib in a patient with von Hippel-Lindau disease: targeting angiogenic factors in pheochromocytoma and other von Hippel-Lindau disease-related tumors. J Clin Endocrinol and Metab. **94**: 386–391.
13 Joshita S, Yoshizawa K, Sano K, Kobayashi S, Sekiguchi T, Morita S, et al (2010). A patient with advanced hepatocellular carcinoma treated with sorafenib tosylate showed massive tumor lysis with avoidance of tumor lysis syndrome. Intern Med. **49**: 991–994.
14 Kloppel G (2011). Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. Endocr-Relat Cancer **18** Suppl 1: S1–S16.
15 Michels J, Lassau N, Gross-Goupil M, Massard C, Mejean A, Escudier B (2010). Sunitinib inducing tumor lysis syndrome in a patient treated for renal carcinoma. Invest New Drugs **28**: 690–693.
16 Morikawa T, Suzuki M, Unno M, Endo K, Katayose Y, Matsuno S (2001). Malignant pheochromocytoma with hepatic metastasis diagnosed 10 years after a resection of the primary incidentaloma adrenal lesion: report of a case. Surg Today **31**: 80–84.
17 Mughal TI, Ejaz AA, Foringer JR, Coiffier B (2010). An integrated clinical approach for the identification, prevention, and treatment of tumor lysis syndrome. Cancer Treat Rev. **36**: 164–176.
18 Nicholaou T, Wong R, Davis ID (2007). Tumour lysis syndrome in a patient with renal-cell carcinoma treated with sunitinib malate. Lancet **369**: 1923–1924.
19 Nomura K, Kimura H, Shimizu S, Kodama H, Okamoto T, Obara T, et al (2009). Survival of patients with metastatic malignant pheochromocytoma and efficacy of combined cyclophosphamide, vincristine, and dacarbazine chemotherapy. J Clin Endocrinol and Metab. **94**: 2850–2856.
20 Oberg K, Castellano D (2011). Current knowledge on diagnosis and staging of neuroendocrine tumors. Cancer Metastasis Rev. **30** Suppl 1: 3–7.
21 Pacak K, Eisenhofer G, Ahlman H, Bornstein SR, Gimenez-Roqueplo AP, Grossman AB, et al (2007). Pheochromocytoma: recommendations for clinical practice from the First International Symposium. October 2005. Nat Clin Pract Endocrinol Metab. **3**: 92–102.
22 Park J, Song C, Park M, Yoo S, Park SJ, Hong S, et al (2011). Predictive characteristics of malignant pheochromocytoma. Korean J Urol. **52**: 241–246.
23 Park KS, Lee JL, Ahn H, Koh JM, Park I, Choi JS, et al (2009). Sunitinib, a novel therapy for anthracycline- and cisplatin-refractory malignant pheochromocytoma. Jpn J Clin Oncol. **39**: 327–331.
24 Safford SD, Coleman RE, Gockerman JP, Moore J, Feldman JM, Leight GS, et al (2003). Iodine -131 metaiodobenzylguanidine is an effective treatment for malignant pheochromocytoma and paraganglioma. Surgery **134**: 956–962.
25 Saylor PJ, Reid TR (2007). Tumor lysis syndrome after treatment of a gastrointestinal stromal tumor with the oral tyrosine kinase inhibitor sunitinib. J Clin Oncol. **25**: 3544–3546.
26 Tanaka S, Ito T, Tomoda J, Higashi T, Yamada G, Tsuji T (1993). Malignant pheochromocytoma with hepatic metastasis diagnosed 20 years after resection of the primary adrenal lesion. Intern Med. **32**: 789–794.
27 Thompson LD (2002). Pheochromocytoma of the Adrenal gland Scaled Score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. Ame J Surg Pathol. **26**: 551–566.
28 Ye L, Santarpia L, Gagel RF (2010). The evolving field of tyrosine kinase inhibitors in the treatment of endocrine tumors. Endocr Rev. **31**: 578–599.
29 Zukauskaite R, Hjorthgau K, Poulsen PL, Baerentzen S, Ladekarl M (2011). Malignant pheochromocytoma and paraganglioma: three cases illustrating the use ofmolecular targeted diagnostics and therapy and possible role of new drugs. Acta Oncol. **50**: 1255–1259.