pISSN 1598-2998, eISSN 2005-9256

Cancer Res Treat. 2014;46(4):411-414

http://dx.doi.org/10.4143/crt.2013.093

Case Report

Open Access

A New Approach to the Treatment of Metastatic Paraganglioma: Sorafenib

Meral Gunaldi, MD[1]
Ismail Oguz Kara, PhD[1]
Berna Bozkurt Duman, MD[1]
Cigdem Usul Afsar, MD[1]
Melek Ergin, PhD[2]
Arbil Avci, MD[2]

Departments of [1]Medical Oncology and [2]Pathology, University of Cukurova Faculty of Medicine, Adana, Turkey

Correspondence: Meral Gunaldi, MD
Department of Medical Oncology,
University of Cukurova Faculty of Medicine,
01330, Saricam-Adana, Turkey
Tel: 90-505-218-0300
Fax: 90-322-338-7072
E-mail: meralgunaldi@gmail.com

Received June 13, 2013
Accepted August 20, 2013

Paragangliomas are relatively rare chromaffin cell tumors which may be cured through resection. Patients with paragangliomas may develop metastatic diseases. There is no consensus regarding refractory chemotherapy for treatment of metastatic disease. In this report, we presented a case of a 43-year-old woman who was admitted to the hospital with a history of episodic headaches, diaphoresis, and weakness. Elevated plasma catecholamine levels and a right paraaortic mass were observed on computed tomography. The mass was excised, and a diagnosis of paraganglioma was confirmed. After 20 months of follow-up, local recurrence and metastases were detected in the thorax, abdomen, and skeletal system. Plasma and urinary catecholamine levels were high. Chemotherapy was administered, and no improvement was observed. Therefore, following this palliative conventional chemotherapy, sorafenib was administered for three months, and, finally, positron emission tomography showed that the patient's lesions had completely regressed.

Key words
Extra-adrenal paraganglioma, Neoplasm metastasis, Sorafenib, Pheochromocytomas, Tyrosine kinase inhibitor

Introduction

Paragangliomas (PGLs), which were first described in 1886 [1], are chromaffin cell tumors that develop from sympathetic and parasympathetic ganglia throughout the abdomen, head and neck area [2]. Some PGLs are inherited, and occur as sporadic tumors. Some hereditary syndromes can be linked to development of PGLs. These syndromes may be von Hippel-Lindau syndrome (VHL) and multiple endocrines neoplasia type 2, and are associated with impaired NF1, RET proto-oncogene or VHL gene expression [3].

In PGL diagnosis, measurement of plasma and urinary metanephrine levels has been used as an effective method. Untreated PGL could have devastating results due to myocardial infarction, severe hypertension, stroke and/or arrhythmia caused by catecholamine excess [2].

Although PGL has been considered as a ten percentage disease (10% metastatic, 10% familial, 10% recurring, 10%

extra-adrenal, 10% occurring in children), up-to-date diagnostic techniques illustrate that this rule of 10% does not indeed accurately describe the disease. PGL patients, with 0-36%, may develop metastatic disease. The familial percentage has been revised to approximately 30% [4]. Extra-adrenal PGLs are reported in patients with a range of 15-20% [2]. In general, PGLs are curable, yet, once a patient presents with metastases, the treatment options become limited.

Case Report

In this report, we present the case of a 43-year-old woman with a history of episodic headaches, diaphoresis, and weakness. Hypertensive and tachycardic episodes were also diagnosed. Detailed family history revealed no unexplained or incompletely explained sudden death. She had elevated plasma and urinary metanephrine/catecholamine levels (Table 1), and a right paraaortic mass (9×9.5 cm) was observed on computed tomography (CT). Preoperatively, α- and β-adrenergic receptor blockers were administered. Following successful resection of the tumor, plasma and 24-hour urinary catecholamine levels were normalized. The mass was excised and diagnosis of PGL was confirmed; synaptophysin and chromogranin were positive (Fig. 1). In postoperative follow-up, the patient's blood pressure and catecholamine levels were normalized.

After 20 months, positron emission tomography (PET) showed local recurrence, and metastases were detected in the thorax, abdomen, and skeletal system (Fig. 2). Plasma catecholamine levels were high (Table 1). An anthracycline plus CVD regimen (adriamycine 7 mg/m^2, dacarbazine 400 mg/m^2, cyclophosphamide 500 mg/m^2, vincristine 1.4 mg/m^2) on days 1 and 2, and zoledronic acid (4 mg) every 21 days were administered, and no improvement was observed on PET following a treatment of six cycles.

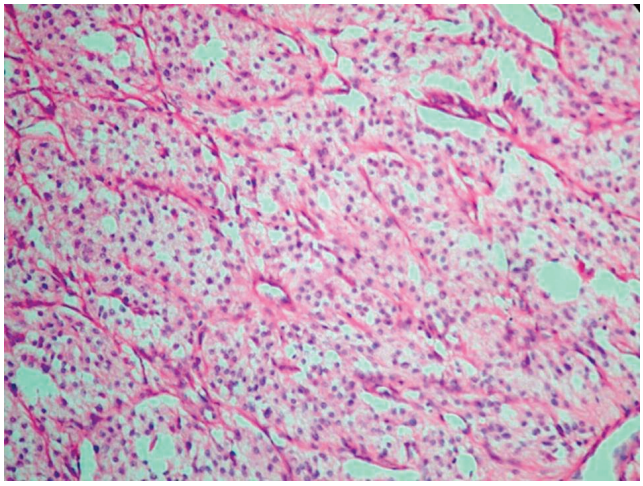

Fig. 1. Zellballen arrangement of the chief cells with peripherally layered sustentacular cells and a prominent capillary network around each group is noted (H&E staining, ×200).

Four months following termination of chemotherapy, calculated plasma and 24-hour urinary catecholamine levels were above normal range. Therefore, sorafenib tosylate (400 mg twice daily) was administered for three months due to recurred-progressive disease. The patient's plasma and 24-hour urinary catecholamine levels finally decreased, and PET/CT showed that metastatic lesions had regressed after 12 weeks (Table 1, Fig. 3). In addition, the patient's symptoms decreased. After 64-week treatment with sorafenib, distance and cerebral metastasis occurred, and the patient died.

Table 1. Plasma and urinary catecholamine levels of patients

	Preoperative	Postoperative	After 20 months	Postchemotherapy	After sorafenib
Plasma					
Epinephrine (< 60 pg/mL)	9	0.3	14	10	11
Norepinephrine (120-680 pg/mL)	206	2.7	2,700	2,100	97
Dopamine (< 87 pg/mL)	1,700	150	2,071	1,800	250
Urinary					
Vanil mandelic acid (3.3-6.5 mg/day)	46	0.8	25	16.8	8.2
Metanephrine (< 350 μg/day)	166	46	214	109	105
Normetanephrine (< 450 μg/day)	1,900	500	2,800	2,599	600

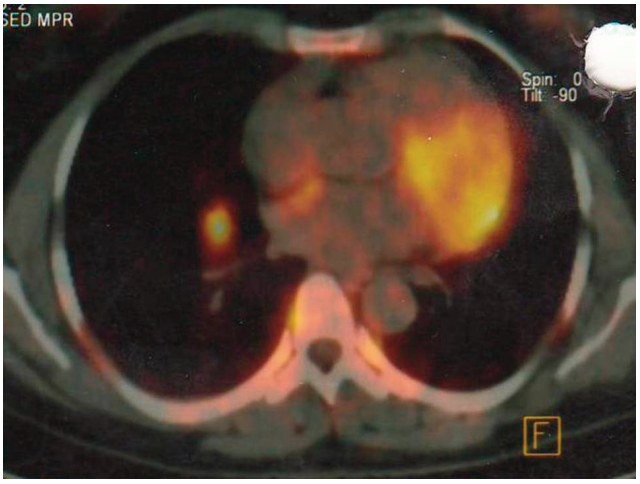

Fig. 2. Positron emission tomography-computed tomography shows metastases.

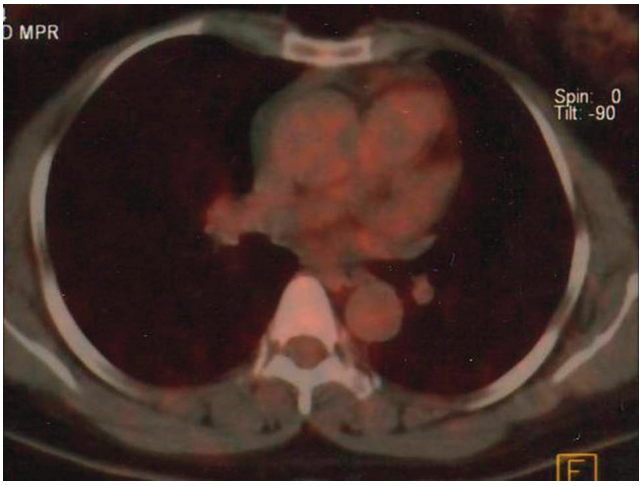

Fig. 3. Positron emission tomography-computed tomography image obtained three months later, after onset of sorafenib therapy, shows regression of all metastases.

Discussion

PGLs, also called extra-adrenal pheochromocytomas, may develop anywhere from sympathetic/parasympathetic nerve cells to major arteries in the body, with 85-90% of occurrence in the abdomen. These tumors, hypersecreting catecholamines, can be observed in any region from the skull to the pelvis. Although metastatic PGLs (mPGLs) have no reliable markers, they can be characterized as being over 5-cm in mass, invading adjacent structures, and spreading to other organs [2].

Options for treatment of mPGLs include palliative tumor resection, ablation, reduction of tumor burden and excess of catecholamine related symptoms, and cytotoxic chemotherapy or targeted agents [5,6].

The benefits of CVD, the most widely used chemotherapeutic regimen [2], appear to be rather short-termed, and exclude an increase in patients' survival [6]. In a recent case study, another chemotherapeutic agent, temozolomide, was reported to yield positive effects prior to tumor resection [7]. Regarding post tumor removal, treatment with targeted radiotherapeutics may yield significant benefits, the most frequent being treatment with ^{131}I-MIBG. The results here suggested that there was a symptomatic response in as many as 67-98% of patients; an observable tumor shrinkage in 27-47%; and a decrease in secretion in 45-67% [2].

So far, treatment with multiple tyrosine kinase inhibitors (mTKI) like sunitinib, to which five patients showed a partial response and one patient showed clinical improvement, appears to be the most effective approach [8-11]. Sunitinib, an oral multitargeted receptor tyrosine kinase inhibitor with antiangiogenic and antitumor activity, targets platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), KIT, and FLT3. Duration of response on sunitinib was 24, 40, 40, 24, 4, and 24 weeks, respectively, in all patients.

Phosphatidylinositide 3-kinase/Akt/mammalian target of rapamycin (mTOR) pathway in the pathogenesis of malignant neuroendocrine tumors includes pheochromocytoma. Everolimus is a compound that inhibits mTOR signalling. Treatment with everolimus, as targeted therapy, was attempted, however, no significant benefits were obtained in four patients [12].

Imatinib does not appear to be useful for treatment of mPGLs; progression was reported in two patients who were administered this drug [13].

Sorafenib, a mTKI, is used in treatment of advanced renal cell and hepatocellular carcinomas. It is an inhibitor of RAF kinase, c-KIT, FLT-3, RET, VEGFRs (VEGFR-2, VEGFR-3), and PDGFR (PDGFR-β). It reduces activation of MEK and MAP kinase, and causes inhibition of cell proliferation, invasion, migration, and tumor growth.

In our case, the patient obtained clinical and laboratory benefits from sorafenib by showing a truly complete response after a three-month therapy. Response duration of sorafenib was 64 weeks in this case. Considering other cases in which sunitinib was administered, this period is quite important. Sorafenib may have potential for treatment of mPGLs since it targets several cellular pathways, one of which is VEGFR-2, -3, and possibly others. High vascularia-

tion is usually a common characteristic in almost all metastatic diseases [2]. Since this is the case, sorafenib may prove to be beneficial in inhibiting vascularization. In addition, expression of the RET gene mutation is known to be the most frequent type in familial PGLs [3]. Sorafenib may also be an active agent in inhibition of the RET proto-oncogene for familial PGLs.

To the best of our knowledge, in the literature, there are no cases with mPGLs subjected to treatment utilizing sorafenib. Because the options for treatment of mPGLs are rather limited, sorafenib may prove to be a very effective agent. The result we obtained with our case is very exciting, yet there is still a need for comprehensive research investigating reliability of this drug in treatment of patients with mPGLs.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

References

1. Frankel F. Ein Fall von doppelseitigem, vollig latent verlaufenen Nebennierentumor und gleichzeitiger Nephritis mit Veranderungen am Circulationsapparat und Retinitis. Virchows Arch. 1886;103:244-63.
2. Fliedner SM, Lehnert H, Pacak K. Metastatic paraganglioma. Semin Oncol. 2010;37:627-37.
3. Krawczyk A, Hasse-Lazar K, Pawlaczek A, Szpak-Ulczok S, Krajewska J, Paliczka-Cieslak E, et al. Germinal mutations of RET, SDHB, SDHD, and VHL genes in patients with apparently sporadic pheochromocytomas and paragangliomas. Endokrynol Pol. 2010;61:43-8.
4. O'Riordain DS, Young WF Jr, Grant CS, Carney JA, van Heerden JA. Clinical spectrum and outcome of functional extraadrenal paraganglioma. World J Surg. 1996;20:916-21.
5. Lehnert H, Mundschenk J, Hahn K. Malignant pheochromocytoma. Front Horm Res. 2004;31:155-62.
6. Zografos GN, Vasiliadis G, Farfaras AN, Aggeli C, Digalakis M. Laparoscopic surgery for malignant adrenal tumors. JSLS. 2009;13:196-202.
7. Kulke MH, Stuart K, Enzinger PC, Ryan DP, Clark JW, Muzikansky A, et al. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. J Clin Oncol. 2006;24:401-6.
8. Joshua AM, Ezzat S, Asa SL, Evans A, Broom R, Freeman M, et al. Rationale and evidence for sunitinib in the treatment of malignant paraganglioma/pheochromocytoma. J Clin Endocrinol Metab. 2009;94:5-9.
9. Jimenez C, Cabanillas ME, Santarpia L, Jonasch E, Kyle KL, Lano EA, et al. 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 Metab. 2009;94:386-91.
10. Park KS, Lee JL, Ahn H, Koh JM, Park I, Choi JS, et al. Sunitinib, a novel therapy for anthracycline- and cisplatin-refractory malignant pheochromocytoma. Jpn J Clin Oncol. 2009;39:327-31.
11. Cirillo F. Metastatic paraganglioma and treatment with sunitinib: a case report. Tumori. 2010;96:1022-7.
12. Druce MR, Kaltsas GA, Fraenkel M, Gross DJ, Grossman AB. Novel and evolving therapies in the treatment of malignant phaeochromocytoma: experience with the mTOR inhibitor everolimus (RAD001). Horm Metab Res. 2009;41:697-702.
13. Gross DJ, Munter G, Bitan M, Siegal T, Gabizon A, Weitzen R, et al. The role of imatinib mesylate (Glivec) for treatment of patients with malignant endocrine tumors positive for c-kit or PDGF-R. Endocr Relat Cancer. 2006;13:535-40.