Case Reports in Oncology

Case Rep Oncol 2020;13:1227–1231
DOI: 10.1159/000510003
Published online: September 30, 2020

Case Report

Durable Response to Pazopanib in Recurrent Metastatic Carotid Body Paraganglioma

Bader Alshamsan[a, b] Jean Paul Atallah[a]

[a]Medical Oncology, Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; [b]Department of Medicine, Qassim Medical College, Qassim University, Qassim, Saudi Arabia

Keywords
Carotid body paraganglioma · Pazopanib · Kinase inhibitor

Abstract
We present the case of a 26-year-old woman living at a high altitude diagnosed initially with nonfamilial and nonsecretory localized carotid body tumor managed with surgery, which developed into a recurrent metastatic tumor treated with cyclophosphamide, vincristine, and dacarbazine. The patient continued to progress and developed a left carotid artery thrombosis and worsening of her systemic symptoms. The patient was re-evaluated, and she decided on no further surgery or systemic therapy. DOTATATE positron emission tomography/computed tomography showed widespread somatostatin-avid disease involving the left carotid bulb mass, bilateral lung nodules, and liver metastases, with the largest in the right hepatic lobe measuring 8 × 7 cm. There were peripancreatic lymph nodes and scattered skeletal metastases. The patient sought a second opinion, on the basis of which she was prescribed pazopanib, to which she showed a dramatic clinical response after 1 month, followed by a durable response for 1 year. Tyrosine kinase inhibitors such as pazopanib are potentially useful in paraganglioma, with further studies needed to understand the role of vascular endothelial growth factor receptor-directed kinase inhibitors in this setting.

Bader Alshamsan
Department of Medicine, Qassim Medical College, Qassim University
PO Box 6655 Airport mail
Buraidah 51432 (Saudi Arabia)
bshmsan@qu.edu.sa

Case Rep Oncol 2020;13:1227–1231
DOI: 10.1159/000510003

Introduction

Carotid body tumors (CBTs) are highly vascular rare neuroendocrine neoplasms [1]. The typical management of CBTs is by surgical resection. However, if a large lesion is fixed or unresectable because of size, radiation therapy is the preferred initial approach. There are no systemic therapies currently approved for patients with malignant paragangliomas [2]. Treatment options are limited, such as combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine with or without doxorubicin (CVD or CyVADIC regimen), iodine-131 meta-iodobenzylguanidine, 177 lutetium peptide (177 Lu-DOTATATE), and vascular endothelial growth factor (VEGF)-directed tyrosine kinase inhibitors (TKIs) such as sunitinib [3, 4]. Other TKIs, such as lenvatinib, cabozantinib, and axitinib, are also undergoing clinical trials [5]. To date, no clinical trials of TKIs have been completed. A phase II study of pazopanib monotherapy in metastatic paraganglioma has been halted due to slow recruitment [6].

We present the first case report of metastatic CBTs demonstrating a durable response to pazopanib and the second case showing a meaningful effect of pazopanib on metastatic paraganglioma [7].

Case Description

A 26-year-old woman living at a high altitude (2,500–2,750 m above sea level) was diagnosed with a CBT after a workup for recurrent syncopal episodes. She underwent excision of a left CBT and carotid artery repair in April 2015. Pathology revealed a 5-cm CBT/paraganglioma with immunohistochemistry positive for synaptophysin and chromogranin with Ki-67 >10%. The CBT had invaded the carotids and nerves, with lymphovascular invasion and positive resection margin. Seven lymph nodes were negative. The patient did not undergo re-resection or adjuvant radiation therapy. Metanephrines and chromogranin A were reported at normal levels. She remained asymptomatic, with no evidence of recurrence until March 2018, when she presented with a nonpainful lump in her left neck, 6 kg weight loss, and a nonproductive cough. Computed tomography (CT) of the head, neck, chest, abdomen, and pelvis revealed a recurrent left carotid mass along with a new bilateral pulmonary nodule, liver, and peripancreatic lymph node involvement. A liver biopsy was performed, which confirmed metastatic paraganglioma.

The patient was started on chemotherapy and completed 2 cycles of CVD in April 2018 before she presented to the emergency department with right-sided weakness. CT head and angiogram of the neck revealed ischemic stroke with left carotid artery thrombosis and recurrence of the tumor. She underwent re-resection with subsequent grafting and was started on anticoagulation with enoxaparin.

The patient was re-evaluated in June 2018 and chose no further therapy, given her systemic symptoms, back pain, and cough had worsened, with DOTATATE positron emission tomography/CT, which revealed widespread somatostatin-avid disease involving the left carotid bulb mass, with bilateral lung nodules, the largest measuring 1.3 cm. The liver metastases were also avid, with the largest in the right hepatic lobe measuring 8 × 7 cm. There were also peripancreatic lymph nodes and scattered skeletal metastases.

The patient sought a second opinion that recommended pazopanib, which was started at the end of June 2018 at an initial dose of 800 mg. She was administered bisphosphonates for her bone metastases. Clinical follow-up at one month revealed a dramatic clinical response with resolution of all her symptoms. She did not tolerate the full dose because of increased liver enzymes and anorexia, so she was kept on 400 mg daily. Regular follow-ups every 2–3 months for almost 1 year revealed excellent clinical response along with imaging showing stable disease by response evaluation criteria in solid tumors (RESIST) (shown in Fig. 1). She

Case Rep Oncol 2020;13:1227–1231
DOI: 10.1159/000510003

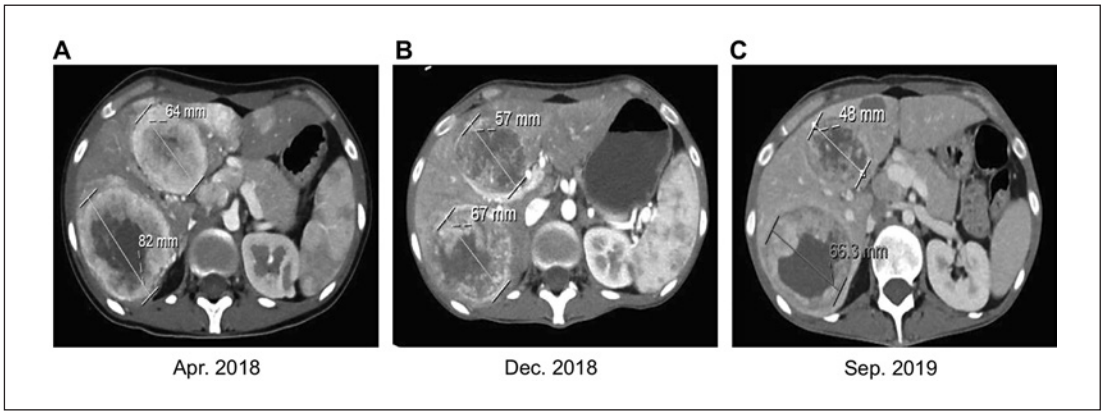

Fig. 1. Computed tomography imaging of the chest at baseline (**A**) in April 2018, after 6 months (**B**), and at 14 months after starting therapy (**C**).

started to relapse clinically and biochemically in November 2019 and eventually developed a clear progression of the disease by December 2019.

Discussion

CBTs, also known as paragangliomas, are highly vascular rare neuroendocrine neoplasms that arise near the carotid bifurcation within glomus cells, embryologically derived from neural crest cells of the autonomic nervous system [8]. Paragangliomas of the head and neck are frequently found in patients aged between 50 and 70 years, but they can occur at any age predominantly in females [9]; its incidence might increase in direct relation to altitude [10]. Most head and neck paragangliomas are benign and not catecholamine secretory. Familial cases are more likely to be secretory and can be bilateral. The criterion of malignancy is made based on the development of metastases rather than histological appearance [11].

Paragangliomas express multiple angiogenic growth factors, including VEGF, that contribute to angiogenesis and carcinogenesis [12]. The signal pathways underlying pathogenesis of these tumors and behind the treatment with TKI are the hypoxia-associated signal pathway regulated by hypoxia-inducible factor and kinase signal pathways [13, 14]. We will review the role of TKIs in this rare malignancy.

Sunitinib is a potent inhibitor of multiple tyrosine kinase receptors, including VEGFR-1 and VEGFR-2, platelet-derived growth factor receptor (PDGFR) beta, KIT, and FMS-like tyrosine kinase 3, and rearranged during transfection. Among 25 patients in an open-label phase II trial of sunitinib in patients with progressive pheochromocytoma and paraganglioma (SNIPP) [4], a disease control rate of 83% was reported (70% with stable disease and 13% with a partial response), with median progression-free survival (PFS) of 13 months. Grade 3 toxicities included fatigue and thrombocytopenia. Three patients discontinued therapy due to hypertension or cardiac events. In another retrospective study, 17 patients with progressive metastatic pheochromocytoma/sympathetic paraganglioma were treated with sunitinib, of whom 14 were evaluable; 3 (21%) demonstrated a partial response and 5 (36%) showed stable disease. Median PFS was 4.1 months. The median overall survival (OS) of the entire group was 27 months [3].

Pazopanib is another kinase inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3, as well as fibroblast growth factors, KIT, and PDGFR, approved for the treatment of patients with

advanced renal cell cancer and advanced soft tissue sarcoma after failure of prior chemotherapy. Pazopanib has been tested in a phase II clinical trial for malignant progressive pheochromocytoma and paraganglioma [6]. The primary endpoint was the best objective response rate. The intervention was pazopanib 400 mg daily for 2 weeks, then 800 mg daily. This study has been halted for poor accrual; 7 patients were recruited. One patient only exhibited a partial response that lasted for approximately 2.4 years. Another patient demonstrated an unconfirmed partial response. The median PFS and OS were 6.5 and 14.8 months, respectively. Several patients had severe adverse effects: 17% had grade 3–4 diarrhea, hematuria, headaches, and fatigue; 50% had severe hypertension, with the toxicity more evident after doubling the dose. Two patients with secretory tumors developed a hypertensive crisis and Takotsubo cardiomyopathy.

Cabozantinib is also active in paragangliomas. Of 14 patients reported by Jimenez [5], 93% had achieved clinical benefit. Hypertension was reported in 40% of the patients, mainly grade 1. The main grade 3 adverse effects were elevated pancreatic enzymes reported in 1 patient, and rectal fistula corrected with surgery reported in another [5].

Axitinib at a starting dose of 5 mg twice daily was evaluated in a phase II clinical trial that enrolled 9 patients. Three achieved partial response, and 5 patients had tumor shrinkage but it was insufficient to meet the RESIST criteria for partial response. Only 1 patient tolerated titration to 7 mg, and 8 patients required a dose reduction [15].

Conclusion

Pazopanib demonstrated clinically meaningful activity in this refractory nonfamilial, nonsecretory, malignant CBT, with a durable response. TKIs are potentially useful, with further studies needed to investigate the efficacy of VEGFR-directed kinase inhibitors in paraganglioma.

Statement of Ethics

Informed consent was obtained from the patient to include treatment history and images in this case report.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

None.

Author Contributions

Bader Alshamsan did the literature review, wrote, and edited the manuscript. He was also involved in patient management. Jean Paul Atallah master supervised the patient management, performed the literature review, and reviewed the manuscript.

References

1 Liu Q, Djuricin G, Staren ED, Gattuso P, Gould VE, Shen J, et al. Tumor angiogenesis in pheochromocytomas and paragangliomas. Surgery. 1996 Dec;120(6):938–43.
2 Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915–42.
3 Ayala-Ramirez M, Chougnet CN, Habra MA, Palmer JL, Leboulleux S, Cabanillas ME, et al. Treatment with sunitinib for patients with progressive metastatic pheochromocytomas and sympathetic paragangliomas. J Clin Endocrinol Metab. 2012 Nov;97(11):4040–50.
4 O'Kane GM, Ezzat S, Joshua AM, Bourdeau I, Leibowitz-Amit R, Olney HJ, et al. A phase 2 trial of sunitinib in patients with progressive paraganglioma or pheochromocytoma: the SNIPP trial. Br J Cancer. 2019 Jun;120(12):1113–9.
5 Jimenez C. Treatment for patients with malignant pheochromocytomas and paragangliomas: a perspective from the hallmarks of cancer. Front Endocrinol (Lausanne). 2018; May;9:277.
6 Jasim S, Suman VJ, Jimenez C, Harris P, Sideras K, Burton JK, et al. Phase II trial of pazopanib in advanced/progressive malignant pheochromocytoma and paraganglioma. Endocrine. 2017 Aug;57(2):220–5.
7 Patel S, Owen D, Schmidt CR, Kirschner LS, Phay J, Shirley L, et al. Favorable and durable response to pazopanib in metastatic refractory paraganglioma. J Oncol Pract. 2017 Dec;13(12):JOP2017024984–2.
8 Jackson CG. Neurotologic skull base surgery for glomus tumors. Diagnosis for treatment planning and treatment options. Laryngoscope. 1993 Nov;103(11 Pt 2 Suppl 60):17–22.
9 Pellitteri PK, Rinaldo A, Myssiorek D, Gary Jackson C, Bradley PJ, Devaney KO, et al. Paragangliomas of the head and neck. Oral Oncol. 2004 Jul;40(6):563–75.
10 Rodríguez-Cuevas S, López-Garza J, Labastida-Almendaro S. Carotid body tumors in inhabitants of altitudes higher than 2000 meters above sea level. Head Neck. 1998 Aug;20(5):374–8.
11 Lam AKY. Update on adrenal tumours in 2017 World Health Organization (WHO) of endocrine tumours. Endocr Pathol. 2017 Sep;28(3):213–27.
12 Jyung RW, LeClair EE, Bernat RA, Kang TS, Ung F, McKenna MJ, et al. Expression of angiogenic growth factors in paragangliomas. Laryngoscope. 2000 Jan;110(1):161–7.
13 Liu Y, Liu L, Zhu F. Therapies targeting the signal pathways of pheochromocytoma and paraganglioma. Onco Targets Ther. 2019 Sep;12:7227–41.
14 Fishbein L, Leshchiner I, Walter V, Danilova L, Robertson AG, Johnson AR, et al. Comprehensive molecular characterization of pheochromocytoma and paraganglioma. Cancer Cell. 2017 Feb;31(2):181–93.
15 Burotto Pichun ME, Edgerly M, Velarde M, Bates SE, Daerr R, Adams K, et al. Phase II clinical trial of axitinib in metastatic pheochromocytomas and paraganlgiomas (P/PG): preliminary results. J Clin Oncol. 2015 Mar;33(7_Suppl):457.