Durable Major Response With Pazopanib in Recurrent, Heavily Pretreated Metastatic Esthesioneuroblastoma Harboring a Fumarate Hydratase Mutation

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INTRODUCTION

Esthesioneuroblastoma (also known as olfactory neuroblastoma) is a rare cancer of neural crest origin that arises in the olfactory epithelium of the upper nasal cavity. It accounts for only 3%-5% of sinonasal tumors.1 Patients commonly present with epistaxis, nasal obstruction, and olfactory and ophthalmic disturbances.2,3 Definitive diagnosis requires both radiography and histopathology. Computed tomography and magnetic resonance imaging (MRI) are used to detail bony involvement and tumor extension to adjacent structures for staging.2 Histologically, esthesioneuroblastoma appears as characteristic nests of small blue cells separated by fibrovascular septa. Immunohistochemistry aids in distinguishing esthesioneuroblastoma from other small, round, blue cell neoplasms occurring in the sinonasal tract, such as lymphoma, Ewing’s tumor, and rhabdomyosarcoma.1

Owing to its rarity and resultant lack of prospective randomized studies to guide therapy, there is currently no defined standard first-line treatment for esthesioneuroblastoma. The generally accepted standard of care is extrapolated from treatment of other head and neck cancers and usually consists of surgery followed by radiation and sometimes chemotherapy,2,4 although neoadjuvant concurrent chemoradiation for locally advanced esthesioneuroblastoma has also been described.3

The clinical course of treated esthesioneuroblastoma is variable, with published 5-year survival rates ranging from 45% to 90%.2,6,7 Recurrences occur within the first 2-3 years in up to 50% of cases, but recurrences are common as far as 5-10 years after initial diagnosis.1,4 Cervical nodal metastasis and distant metastasis occur in 25% and 10% of cases, respectively.1,8 For recurrent or progressive disease after initial therapy, systemic chemotherapy has been disappointing.2,8 The introduction of biologically targeted agents, including small molecules and monoclonal antibodies, has provided additional treatment options for many cancers, including esthesioneuroblastoma. Several case reports have shown success with these agents,10 and we add to the growing evidence base by presenting a case of recurrent metastatic esthesioneuroblastoma in which a prolonged partial response was achieved with pazopanib for over 4 years and ongoing as of this report.

Pazopanib is an oral multi-tyrosine kinase inhibitor (TKI) that targets angiogenesis by inhibiting vascular endothelial growth factor receptors (vascular endothelial growth factor receptor [VEGFR]-1, -2, and -3), platelet-derived growth factor receptors (platelet-derived growth factor receptor-α and -β), stem cell factor receptor (c-KIT), and fibroblast growth factor receptor-1 and -3.11 It is approved by the US Food and Drug Administration for treatment of renal cell carcinoma and certain types of soft tissue sarcoma.12,13

CASE REPORT

This 69-year-old woman developed anosmia and persistent rhinorrhea in 1994. She was referred to an otolaryngologist who removed a tumor from the upper nasal cavity, and pathology demonstrated esthesioneuroblastoma. She underwent complete resection of the tumor and completed a 4-week course of adjuvant radiation therapy (40 Gy in 20 fractions). She had regular follow-up until she developed a nodule in her left temple in 2004, which was excised and demonstrated recurrent disease. She subsequently experienced multiple recurrences and was referred to medical oncology. She received four cycles of chemotherapy with cisplatin 60 mg/m2 and etoposide 120 mg/m2 to prevent further relapse. A positron emission tomography-computed tomography in 2009 showed no evidence of disease. She had regular follow-up until she developed a nodule in her left arm in 2004, which was excised and demonstrated recurrent disease. She subsequently underwent complete resection of the tumor and completed a 4-week course of adjuvant radiation therapy (40 Gy in 20 fractions). She had regular follow-up until she developed a nodule in her left temple in 2004, which was excised and demonstrated recurrent disease. She subsequently experienced multiple recurrences and was referred to medical oncology. She received four cycles of chemotherapy with cisplatin 60 mg/m2 and etoposide 120 mg/m2 to prevent further relapse. A positron emission tomography-computed tomography in 2009 showed no evidence of disease. In 2011, recurrent lesions were excised and she was treated with chemoradiotherapy with weekly carboplatin and paclitaxel and concurrent radiation therapy for 30 days (60 Gy in 30 fractions). Additional recurrent lesions were resected in 2013 and 2015.

An MRI in December 2016 revealed increasing size of masses in the right buccal and masticator space, left masticator space, scalp, as well as increased size of a...
A dural-based mass in the bilateral anterior cranial fossa floor and vasogenic edema in bilateral frontal lobes (Fig 1A). Her case was reviewed at a multidisciplinary tumor board, and it was determined that these disease sites were no longer resectable. Using the Caris Molecular Intelligence platform (Caris Life Sciences, Phoenix, AZ), tumor specimen
obtained in November 2015 was analyzed for 592 genes and revealed a presumed pathogenic mutation in fumarate hydratase (FH; Table 1). However, no clear actionable targets or applicable clinical trials were identified. By this time, the patient had a markedly swollen face, which was alarming to her.

The patient then started pazopanib 400 mg oral daily dose. Within a week, she noted rapid decrease in facial edema and size of the lesions on her forehead and right mouth. On therapy, she developed decreased appetite, fatigue, and myalgias as well as dryness in her hands, which led to a dose reduction of pazopanib to 200 mg daily. Follow-up MRI brain showed significant response at her disease sites consistent with partial response (Fig 1B). Her most recent surveillance imaging in October 2020 demonstrated stable disease. This represents durable partial response of metastatic esthesioneuroblastoma on pazopanib therapy for 4 years and ongoing. A timeline of her disease course and treatments is included in Figure 2. Written consent was provided by the patient for publication of her clinical information and images as a case report.

DISCUSSION

As a rare malignancy, esthesioneuroblastoma currently has no defined treatment regimen. At diagnosis, multimodality therapy (surgery, radiation, and chemotherapy) is typically used. For recurrent or progressive disease, cytotoxic chemotherapy has been only modestly effective. Several recent case reports describe successful use of targeted therapy with small molecules and/or monoclonal antibodies in treatment of recurrent metastatic esthesioneuroblastoma (Table 2). Preusser et al\(^6\) reported on a 69-year-old man with massive progression of metastatic esthesioneuroblastoma following surgical resection and radiation therapy who achieved disease stabilization for 15 months with the TKI sunitinib before passing away from an unrelated traumatic injury. Wang et al\(^3\) used whole-exome sequencing to identify gene targets for treatment of a 44-year-old man with recurrent metastatic esthesioneuroblastoma.
following surgical resection, radiation therapy, and platinum-based chemotherapy who achieved clinical response with sunitinib and cetuximab. Dunbar et al. reported on a 60-year-old man with recurrent metastatic esthesioneuroblastoma following treatment 17 years earlier with surgical resection, radiation therapy, and both platinum-based and non–platinum-based chemotherapy who ultimately achieved stable disease for 22 months with the anti-angiogenic agent bevacizumab. Kim et al. reported on a 46-year-old man with an extensive locally infiltrating frontobasal tumor who underwent surgical resection and radiation therapy followed by cisplatin and etoposide with multiple subsequent recurrences who ultimately achieved prolonged partial remission with imatinib after his tumor was determined to be immunohistochemically positive for c-KIT. Fury et al. conducted a phase I study using everolimus and cisplatin in patients with advanced solid tumors; the results included one subject with esthesioneuroblastoma previously treated with radiation who achieved prolonged stable disease. Gay et al. performed comprehensive genomic profiling on samples from 41 cases of esthesioneuroblastoma, including one from a 49-year-old woman who underwent surgical resection and radiation therapy for disease of paranasal sinus with subsequent distant metastasis who achieved stable disease for 2 years on pazopanib and docetaxel.

As precision medicine is increasingly used, use of targeted drugs for treating recurrent metastatic esthesioneuroblastoma is likely to increase. The antineoplastic effect of pazopanib and other multi-TKIs is presumably through inhibition of VEGF receptors and additional growth receptors involved in angiogenesis. Specifically in regards to the presented patient, we postulate that her significant response to pazopanib is related to her presumed pathogenic FH mutation. FH is an enzyme catalyzing the hydration of fumarate to malate in the Kreb’s cycle. Mutations of FH lead to accumulation of excess fumarate, which then inhibits hypoxia-inducible factor (HIF) prolyl hydroxylase. HIF prolyl hydroxylase facilitates ubiquitination and degradation of HIF; therefore, its inhibition results in stabilization and accumulation of HIF. HIF genes are involved in regulating angiogenesis through upregulation of downstream genes, which include VEGF. Increased VEGF transcription produced by this complex chain of inhibition and upregulation of genes in patients with FH mutations serves as an appealing therapeutic target for agents such as pazopanib, which inhibit VEGF receptors as part of their antiangiogenic mechanism. Although pazopanib predominantly exerts its effect through inhibition of VEGFR, platelet-derived growth factor receptor, and c-KIT, it was also shown to inhibit fibroblast growth factor receptor in vitro and it is plausible that this mechanism of action contributes to the antitumor effect in our case since she also harbors amplification of FGF3 and FGF4 ligands.

Mutation of FH in esthesioneuroblastoma was previously reported. Although confirmation by germline genetic testing would be needed, the high percentage of our patient’s tumor cells containing an FH mutation suggests a germline mutation, although she does not have a personal or family history suggestive of a germline FH defect.

| TABLE 1. Summary of Caris Findings |
| Gene | Aberration (% Tumor Cells) | Method |
| CCND1 | Amplified | NGS |
| CDH1 exon 14 | D756Y Mutated, variant of unknown significance (16) | NGS |
| FGF3 | Amplified | NGS |
| FGF4 | Amplified | NGS |
| FH exon 10 | K477dup Mutated, presumed pathogenic (85) | NGS |
| TUBB3 | Positive (65) | IHC |

Abbreviations: FH, fumarate hydratase; IHC, immunohistochemistry; NGS, next-generation sequencing.
date, she has enjoyed a durable partial response for 48 months. If she experiences progressive disease, the next line of treatment could include a selective inhibitor of circulating VEGF such as bevacizumab, in keeping with our suspicion that her current prolonged disease control is through an antiangiogenic pathway.

Case reports and cohort studies add to the growing fund of knowledge and are valuable in real-world management of this rare malignancy after recurrence. They suggest that biologic targeted therapies can have a durable impact on even heavily pretreated patients with esthesioneuroblastoma.

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