

Case Report

Clinical Benefit from Trametinib in a Patient with Appendiceal Adenocarcinoma with a *GNAS R201H* Mutation

Celina Ang^a Aryeh Stollman^b Hongfa Zhu^c Umut Sarpel^d
Bethann Scarborough^e Gagan Sahni^f Sherri Z. Millis^g

^aDivision of Hematology/Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ^bDepartment of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ^cDepartment of Anatomic Pathology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ^dDepartment of Surgery, Division of Surgical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ^eBrookdale Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ^fDivision of Cardiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ^gFoundation Medicine, Inc., Cambridge, MA, USA

Keywords

Appendiceal adenocarcinoma · Targeted therapy · *GNAS* mutation · Trametinib

Abstract

We report the case of a patient with appendiceal adenocarcinoma with mucinous peritoneal carcinomatosis who was treated with trametinib upon identification of a *GNAS R201H* mutation by comprehensive genomic profiling. The molecular pathology of appendiceal neoplasms is reviewed, and the mechanistic basis underlying the clinical benefit as well as the subsequent course on trametinib that were observed in this patient are discussed.

© 2017 The Author(s)
Published by S. Karger AG, Basel

Introduction

Appendiceal neoplasms are rare, occurring in <1.5% of appendectomy specimens [1]. Histologic variants include adenocarcinomas, low- and high-grade mucinous neoplasms, goblet cell carcinoids, and neuroendocrine tumors [1, 2]. Pseudomyxoma peritonei (PMP) results from peritoneal dissemination of mucinous appendiceal neoplasms [2]. Surgery is indicated for early-stage disease, and in patients with PMP, aggressive cytoreductive surgery with hyperthermic intraperitoneal chemotherapy can yield durable disease control [3]. For unresectable or metastatic appendiceal adenocarcinoma, systemic therapy following colorectal paradigms is the mainstay, though clinical trial data are limited [4]. Comprehensive genomic profiling (CGP) offers the promise of personalized therapy and may yield clinical benefit when standard chemotherapies are no longer effective. We present a patient with a mucinous appendiceal adenocarcinoma and PMP refractory to several conventional chemotherapy agents who experienced clinical benefit from trametinib based on CGP results demonstrating a *GNAS R201H* mutation.

Case Presentation

A 53-year-old man previously in good health developed abdominal distension. Computed tomography (CT) showed a dilated appendix measuring 9.4 × 4.4 cm and large-volume gelatinous ascites with extensive peritoneal carcinomatosis measuring up to 3.0 cm in thickness, consistent with PMP from a mucinous appendiceal neoplasm. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy were attempted but aborted as optimal debulking could not be achieved. Peritoneal cytology and omental specimens revealed a disseminated well-differentiated mucinous adenocarcinoma expressing CK20, CDX-2, MLH1, MSH2, MSH6, and PMS2, and wild-type *KRAS* and *BRAF*. The patient started FOLFIRINOX chemotherapy given his age and good functional status. Baseline serum CA 19-9 and CEA were 449.8 U/mL and 3.1 ng/mL, respectively. His disease remained stable on therapy for 6 months, with a slight decrease in ascites and a decrease in CA 19-9 to 226.5 U/mL and in CEA to 2.0 ng/mL. CA 125, not previously checked, was 29 U/mL. Due to worsening oxaliplatin neuropathy he switched to FOLFIRI + bevacizumab for 6 months. Repeat CT of the chest, abdomen, and pelvis showed an 8.4 × 4.6 cm appendiceal mass and a 2.6 cm peritoneal carcinomatosis. However, his CA 19-9 increased acutely to 4,730.6 U/mL, CA 125 to 64 U/mL, and CEA to 6.4 ng/mL. Given the cumulative side effects from treatment and absence of disease-related symptoms, following extensive discussion, the patient took a 2-month break from chemotherapy. In the interim his CA 19-9 and CEA rose to 7,805.5 U/mL and 20.5 ng/mL, respectively, though his disease remained grossly stable radiographically. Irinotecan + panitumumab was started, but his disease progressed after 3 months with a commensurate rise in CA 19-9 to 8,463.7 U/mL and a slight decrease in CEA to 17.9 ng/mL. On CT, the appendiceal mass was stable and the peritoneal thickness was 1.8 cm, but the extent of carcinomatosis had increased, and the patient required admission for pain and management of ascites. A large-volume paracentesis was unsuccessful because of extensive loculation. An intraperitoneal catheter was subsequently placed, draining approximately 100 mL of serosanguinous fluid daily. Given continued progression after 18 months of standard chemotherapy, archived omental tissue was submitted to a CLIA-certified, CAP-accredited laboratory (Foundation Medicine, Inc., Cambridge, MA) for CGP. This revealed an activating *GNAS R201H* mutation. Though no clinical studies have directly

linked *GNAS* mutations in cancer to targeted therapies, preclinical evidence suggests that tumors with *GNAS* mutations may be sensitive to MAPK and Wnt pathway inhibitors [5]. Trametinib is an FDA-approved noncompetitive inhibitor of ATP which binds MEK adjacent to the ATP binding site, similar to other MEK allosteric inhibitors, thus inhibiting RAF-dependent phosphorylation of MEK1 [6]. It was thus decided to treat the patient with the MEK inhibitor trametinib 2 mg daily.

The patient underwent a baseline ophthalmologic assessment and radionuclide ventriculography which showed normal biventricular size and function as well as a left ventricular ejection fraction (LVEF) of 50%. Within the first 2 weeks of therapy, he developed a grade 2 acneiform rash affecting the face, upper chest, and back, as well as lower extremity edema. Drainage from his peritoneal catheter slowly decreased and eventually ceased. After 2 months, his CA 19-9 had decreased to 4,428.7 U/mL, CEA to 6.5 ng/mL, and CA 125 to 38 U/mL. On repeat CT, his appendiceal mass was 7.4 × 4.5 cm and the peritoneal carcinomatosis was stable. Although his peritoneal catheter had stopped draining 2 months earlier, his abdominal girth remained stable without reaccumulation of ascites. His analgesic requirements also decreased from MS Contin 30 mg every 8 h and morphine 10 mg every 4 h at the start of trametinib to morphine 10 mg prn. Repeat echocardiography performed because of persistent lower extremity edema showed a decrease in LVEF to 40% which was attributed to trametinib since his pretreatment LVEF had been 50% 3 months earlier. After discussion of the risks and benefits of continuing trametinib in light of his cardiac dysfunction and considering the fact that he was asymptomatic apart from edema, he continued trametinib at a reduced dose of 1 mg daily. Given stability of his symptoms and LVEF 1 month later, trametinib was increased to 1.5 mg daily. Tumor markers remained stable 3.5 months after starting trametinib: CA 19-9 was 4,624.5 U/mL, CEA was 6.2 ng/mL, and CA 125 was 21 U/mL. One month later, he was admitted for persistent nausea, vomiting, and poor oral intake. Repeat imaging demonstrated a partial small bowel obstruction but no significant change in overall disease burden. He was evaluated by gastroenterology and surgical oncology, but his disease was not amenable to stent placement nor venting gastrostomy. After extensive discussions, the patient decided to discontinue therapy and return to his home country.

Discussion

The molecular topography of mucinous appendiceal neoplasms is characterized by *KRAS* mutations in 40–78% of cases and by alterations in *APC*, *ATM*, *PIK3CA*, *SMAD4*, *NRAS*, *GNAS*, *TP53*, and the *TGF-β* pathway, particularly in adenocarcinomas [7, 8]. *GNAS* mutations are primarily the hallmark of low-grade appendiceal mucinous neoplasms (24–82%), but have also been reported in low-grade/well-differentiated adenocarcinomas (22–35%) and in high-grade adenocarcinomas with (15%) and without signet rings (37%) [7–12]. *GNAS* encodes the alpha subunit of the stimulatory G protein (Gs-alpha), a guanine-nucleotide binding protein (G protein) involved in hormonal regulation of adenylate cyclase [13]. *R201H* is an activating mutation causing increased Gnas/XLαs activity, increased cAMP accumulation, and constitutive cAMP signaling, associated with excessive proliferation and tumor development [5, 13, 14]. Clinically, *GNAS* activation may be responsible for the copious mucin production associated with PMP [10]. The demographics, presence or absence of adverse pathologic features, and survival outcomes of patients with appendiceal neoplasms do not appear to be impacted by *GNAS* mutation status [11, 12].

Since *GNAS* activation may affect downstream MAPK and Wnt signaling pathways [5], inhibitors of these pathways, such as trametinib, may be relevant to tumors with *GNAS*-activating mutations.

Our patient experienced meaningful, albeit short-lived, clinical benefit – including an improvement in quality of life – from trametinib, suggesting that targeted MAPK pathway inhibition was important in inducing tumor response. His time to progression of about 4 months on trametinib is comparable to the median progression-free survival of 4.8 months reported in patients with *BRAF*-mutated melanoma [15]. The dose reduction in trametinib because of cardiotoxicity prompts speculation about whether this might have shortened the duration of his clinical response. Based on preclinical data, the target plasma trametinib concentration for MEK pathway inhibition is 10.4 ng/mL [15, 16]. Trametinib 2 mg daily exceeds this target concentration throughout the dosing period, whereas a 1-mg daily dose yields concentrations that mostly remain below this threshold [17]. Pharmacokinetic analysis from a phase 2 study of trametinib reported a shorter progression-free survival in patients with median plasma trametinib concentrations <10.6 ng/mL than in those with concentrations ≥10.6 ng/mL [15].

To our knowledge, this is the first case of an appendiceal mucinous neoplasm treated with trametinib for *GNAS* alteration, highlighting the clinical potential of personalized, targeted therapy in rare malignancies.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

S.Z.M. is an employee of Foundation Medicine, Inc. The other authors have no conflicts of interest to disclose.

References

- 1 Turaga KK, Pappas SG, Gamblin T: Importance of histologic subtype in the staging of appendiceal tumors. *Ann Surg Oncol* 2012;19:1379–1385.
- 2 Carr NJ, Cecil TD, Mohamed F, et al: A consensus for classification and pathologic reporting of pseudomyxoma peritonei and associated appendiceal neoplasia: the results of the Peritoneal Surface Oncology Group International (PSOGI) modified Delphi process. *Am J Surg Pathol* 2016;40:14–26.
- 3 Verwaal VJ, Bruin S, Boot H, et al: 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2008;15:2426–2432.
- 4 Tejani MA, ter Veer A, Milne D, Ottesen R, Bekaii-Saab T, Benson AB 3rd, Schrag D, Shibata S, Skibber J, Weiser M, Wilkinson N, Cohen SJ: Systemic therapy for advanced appendiceal adenocarcinoma: an analysis from the NCCN Oncology Outcomes Database for colorectal cancer. *J Natl Compr Canc Netw* 2014;12:1123–1130.
- 5 Wilson CH, McIntyre RE, Arends MJ, Adams DJ: The activating mutation R201C in *GNAS* promotes intestinal tumorigenesis in *Apc(Min/+)* mice through activation of Wnt and ERK1/2 MAPK pathways. *Oncogene* 2010;29:4567–4575.
- 6 Gilmartin AG, Bleam MR, Groy A, et al: GSK1120212 (JTP-74057) is an inhibitor of MEK activity and activation with favorable pharmacokinetic properties for sustained in vivo pathway inhibition. *Clin Cancer Res* 2011;17:989–1000.

- 7 Liu X, Mody K, de Abreu FB, et al: Molecular profiling of appendiceal epithelial tumors using massively parallel sequencing to identify somatic mutations. *Clin Chem* 2014;60:1004–1011.
- 8 Noguchi R, Yano H, Gohda Y, et al: Molecular profiles of high-grade and low-grade pseudomyxoma peritonei. *Cancer Med* 2015;4:1809–1816.
- 9 Hara K, Saito T, Hayashi T, et al: A mutation spectrum that includes *GNAS*, *KRAS* and *TP53* may be shared by mucinous neoplasms of the appendix. *Pathol Res Pract* 2015;211:657–664.
- 10 Alakus H, Babicky ML, Ghosh P, et al: Genome-wide mutational landscape of mucinous carcinomatosis peritonei of appendiceal origin. *Genome Med* 2014;6:43.
- 11 Nishikawa G, Sekine S, Ogawa R, Matsubara A, Mori T, Taniguchi H, Kushima R, Hiraoka N, Tsuta K, Tsuda H, Kanai Y: Frequent *GNAS* mutations in low-grade appendiceal mucinous neoplasms. *Br J Cancer* 2013;108:951–958.
- 12 Singhi AD, Davison JM, Choudry HA, et al: *GNAS* is frequently mutated in both low-grade and high-grade disseminated appendiceal mucinous neoplasms but does not affect survival. *Hum Pathol* 2014;45:1737–1743.
- 13 Mariot V, Wu JY, Aydin C, et al: Potent constitutive cyclic AMP-generating activity of *XLas* implicates this imprinted *GNAS* product in the pathogenesis of McCune-Albright syndrome and fibrous dysplasia of bone. *Bone* 2011;48:312–320.
- 14 Landis CA, Masters SB, Spada A, et al: GTPase inhibiting mutations activate the alpha chain of Gs and stimulate adenylyl cyclase in human pituitary tumours. *Nature* 1989;340:692–696.
- 15 Flaherty KT, Infante JR, Daud A, et al: Combined *BRAF* and *MEK* inhibition in melanoma with *BRAF* V600 mutations. *N Engl J Med* 2012;367:1694–1703.
- 16 Ouellet D, Kassir N, Chiu J, Mouksassi MS, Leonowens C, Cox D, DeMarini DJ, Gardner O, Crist W, Patel K: Population pharmacokinetics and exposure-response of trametinib, a *MEK* inhibitor, in patients with *BRAF* V600 mutation-positive melanoma. *Cancer Chemother Pharmacol* 2016;77:807–817.
- 17 Infante JR, Fecher LA, Falchook GS, et al: Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral *MEK* inhibitor trametinib: a phase 1 dose-escalation trial. *Lancet Oncol* 2012;13:773–781.