Case Report

A case of class 3 MEK1 mutated metastatic colorectal cancer with a non-durable tumor marker response to MEK and ERK inhibitors

Chongkai Wang, Jaideep Sandhu, Marwan Fakih

Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

Correspondence to: Marwan Fakih, MD. Professor, Medical Oncology and Therapeutics Research; Judy and Bernard Briskin Distinguished Directorship in Clinical Research; Medical Director, Briskin Center for Clinical Research; Section Head, GI Medical Oncology, City of Hope Comprehensive Cancer Center, Building 51, Room 112, 1500 E Duarte St, Duarte, CA 91010, USA. Email: mfakih@coh.org.

Abstract: Class 3 MEK1 mutations disrupt the negative regulatory helix region of MEK1 and drive constitutive activation of both pMEK and pERK that is independent of RAF and of MEK phosphorylation. Targeting MEK with trametinib resulted in mixed clinical responses in class 3 MEK1 mutated Langerhans cell histiocytosis (LCH). The ERK inhibitor, ulixertinib, demonstrated limited anti-tumor activity in non-characterized MEK1 mutated solid tumors, with 2 out 4 patients experiencing stable disease (SD). Here, we present the case of a 52-year-old female with metastatic colon cancer harboring a MEK1E102_I103del (class 3 mutation) who progressed on standard chemotherapy and showed no response to the MEK inhibitor trametinib, the ERK inhibitor ulixertinib, and the combination of ulixertinib and the anti-EGFR antibody panitumumab. Despite progressive disease (PD), the patient exhibited a steep but short-lived tumor marker response to MEK and ERK inhibition, suggesting the emergence of early mechanisms of resistance to MAPK pathway inhibition. This report presents the first case in the literature investigating a MEK inhibitor and an ERK inhibitor (alone and in combination with anti-EGFR therapy) in metastatic colorectal cancer harboring a class 3 MEK1 mutation (E102-I103 deletion).

Keywords: MEK1 mutation; MEK inhibitor; ERK inhibitor; anti-EGFR

Submitted May 07, 2019. Accepted for publication Jul 26, 2019.
doi: 10.21037/jgo.2019.08.02
View this article at: http://dx.doi.org/10.21037/jgo.2019.08.02

Case presentation

A 52-year-old female presented with obstructive symptoms and abdominal pain, which led to a diagnosis of descending colon adenocarcinoma with metastatic disease to the lungs, liver and retroperitoneal lymph nodes. Left hemicolectomy revealed a poorly differentiated adenocarcinoma with signet-ring and mucinous features. She received first-line chemotherapy with FOLFOX for 5 cycles with stable disease (SD) as best response. In the interim, next generation sequencing (NGS) of her primary tumor by FoundationOne® (Gene List: https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx, Foundation Medicine, Inc., Cambridge, MA, USA) revealed a microsatellite stable, KRAS and NRAS wild type, BRAF wild type, IDH1 R132c [mutation allele frequencies (MAF) 22.18%] mutation, FANCG loss exons 5–14, GNAS R201H (MAF, 38.69%), and aMEKI (E102-I103del, MAF, 21.87%) mutation. Given the lack of RAS and BRAF mutations and the concerns about prior anastomotic microperforation, panitumumab was added to her treatment regimen. She progressed after an additional 4 cycles of FOLFOX plus panitumumab chemotherapy. Given her refractoriness to first-line chemotherapy and emerging case reports of MEK1 mutated tumors responding to MEK inhibitor, she was treated with trametinib (1-3). She experienced a short-lived decline in CA19.9 (Figure 1A). Unfortunately, she had progressive disease (PD) on CT scan after 3 months of trametinib treatment. She was then
treated with FOLFIRI plus bevacizumab with SD as best response, followed by PD at after 5 months of treatment. Given emerging pre-clinical data characterizing MEKI (E102_I103) mutation as a class 3 MEKI mutation with relative resistance to MEK inhibitors and with sensitivity to ERK inhibitors, we treated our patient on a single-patient Investigational New Drug (IND)-exempt clinical trial of the ERK inhibitor, ulixertinib (BVD-523) (4-6). The study was approved by City of Hope Investigational Review Board (IRB #18278). Ulixertinib was administrated orally twice-daily at the previously recommended phase II dose of 600 mg PO BID (6). Two weeks after initiation of ulixertinib, the patient experienced a more robust, but short-lived, decline in CA19.9 (Figure 1B). The treatment was well-tolerated with mild to moderate nausea, fatigue, and dry skin (grade 1). Unfortunately, she experienced a subsequent surge in tumor markers and radiographic progression following 6 weeks of treatment. Meanwhile, digital NGS of cell-free DNA (cfDNA) carried out by Guardant360 cfDNA assay (Gene List: http://www.guardant360.com/, Guardant Health, Redwood City, CA, USA) revealed an increased proportion of MEKI cfDNA (0.095589–1.41%), GNAS R201H cfDNA (0.3–2.5%), IDH1 R132C cfDNA (0.1–1.1%), and MET (non-detectable–0.1%), with the detection of a synonymous PIK3CA mutation, which suggests increased tumor load and tumor evolution but without clear explanation of the resistance mechanisms (Figure 1C). Given the concern that the rapid acquired resistance was related to compensatory EGFR phosphorylation, we amended her clinical trial to allow for the combination of ulixertinib plus panitumumab. Following IRB approval and after obtaining patient consent, ulixertinib was continued at 600 mg PO BID in combination

Figure 1 Tumor markers and cfDNA changes following treatment. (A) CA19.9 and CEA levels following trametinib treatment. Trametinib was started on 11/7/2017 and ended on 2/14/2018; (B) CA19.9 and CEA levels following ulixertinib treatment. Ulixertinib was started on 8/1/2018, and ended on 9/4/2018; (C) cfDNA alterations before and after ulixertinib monotherapy; (D) CA19.9 and CEA level following ulixertinib plus panitumumab treatment. Ulixertinib plus panitumumab were started on 9/6/2018 and ended on 9/19/2018. cfDNA, cell-free DNA.
with panitumumab 6 mg/kg given intravenously every 2 weeks. Unfortunately, this treatment was poorly tolerated with refractory nausea and vomiting requiring admission following 2 weeks of treatment. Imaging studies at the time of admission did not show any obstructive findings and her disease burden was noted to be unchanged in this short period of treatment. Given the intolerance to protocol treatment and lack of disease regression or tumor marker decline (Figure 1D) with ulixertinib plus panitumumab, the patient was taken off study. She was subsequently treated with trifluridine/tipiracil with rapid disease progression and death.

Discussion

Mutations in MEK1 occur in approximately 1–2% of colorectal cancer patients, and have been characterized as oncogenic (7,8). Preclinical studies confirm that MEK1 activating mutations are sufficient to transform intestinal epithelial cells and facilitate the formation of high-grade adenocarcinoma (9). MEK1 mutations have been classified into 3 classes. Class 1 MEK1 mutations are RAF-dependent and are the least activating. Class 2 MEK1 mutations are activating in nature but can be upregulated further by upstream RAF. Class 3 MEK1 mutations (∆L98-I103, ∆I99-K104, ∆E102-I103, ∆I103-K104) lead to auto-phosphorylation of MEK which is independent of RAF and are associated with the highest level of downstream ERK phosphorylation (4). Class 3 MEK1 mutations are mutually exclusive with other mutations that activate MAPK signaling, and are therefore considered driver mutations. In addition, class 3 mutations promote tumor formation in mice more efficiently than class 1 and class 2 mutations, suggesting that this class is the most oncogenic amongst MEK1 mutations (4). Among solid tumors, MEK1 mutations have been best characterized in non-small cell lung cancer (NSCLC), where class 2 mutations (K57N and Q56P) were the most common and were associated with a worse outcome in the setting of metastatic colorectal disease (10).

Gao et al. have previously demonstrated the relative resistance of class 3 MEK1 mutations to MEK inhibition (4). Prior to Gao’s report, we treated our patient with trametinib, and her disease indeed progressed after 3 months of trametinib. However, trametinib was associated with complete remission in a case of class 3 MEK1 mutation (∆E102-I103) Langerhans cell histiocytosis (LCH) and with PD in another class 3 MEK1 mutation (∆L98- K104) LCH patient (3,11). Complete responses to MEK inhibitors have also been described in two cases with histiocytic sarcoma and serous ovarian cancer, both harboring class 2 MEK1 mutations (1,2).

Given this patient’s resistance to multiple lines of chemotherapy and to trametinib, and in light of pre-clinical and clinical work suggesting benefit from ERK inhibition (4,6). We treated our patient with ulixertinib alone and added panitumumab to ulixertinib at the time of progression, on a single patient IND-exempt clinical trial. In line with our expectations, treatment with ulixertinib resulted a steeper decline in CA19.9 than with trametinib, but this response was short lived and disease progression was recorded four weeks after starting ulixertinib. CEA and CA19.9 tumor markers are often elevated in the setting of metastatic colorectal cancer. Comparative studies between CEA and imaging studies show a very strong correlation between CEA response and imaging response. Combining with the initial decline of CEA and subsequent rise in those markers, our results suggest an initial response with rapid onset of acquired resistance to ERK inhibition (12). Circulating cfDNA assays showed an emergent PIK3CA mutation at the time of resistance. This specific mutation causes a synonymous alteration which is not likely the underlying mechanism of resistance. Adding panitumumab to her treatment did not reverse this resistance, which suggests that the mechanism of resistance is not likely limited to compensatory EGFR phosphorylation. Unfortunately, no serial tumor biopsies were obtained during treatment, making the mechanistic evaluation of resistance more challenging.

Disparity in sensitivity to BRAF inhibitors between melanoma and colorectal cancer suggests primary tumor heterogeneity despite harboring identical BRAF mutations (13,14). This case highlights similar heterogeneity in response to MEK or ERK inhibitors within MEK1 mutated tumors and highlights the need of better pre-clinical models to guide drug development in this rare molecularly defined subgroup. While similar mutations to our case have responded to MEK inhibition in the setting of LCH, no clinical response was noted in our case with either MEK inhibitors or ERK inhibitors +/- anti-EGFR. The initial response in tumor markers followed by rapid disease progression suggests rapid compensatory mechanisms that bypass in MEK and ERK inhibition in CRC. Future studies investigating ERK or MEK inhibitors in tumors harboring MEK1 mutations should include robust correlative studies and PDX modeling to better delineate the various mechanisms of resistance and to develop better rational...
combinations for this patient population.

Acknowledgments

None.

Footnote

Conflicts of Interest: M Fakih: Amgen [Honoraria, Advisory/Consultancy, Speaker Bureau/Expert Testimony, Research Grant (Institution)], Array (Advisory/Consultancy), Bayer (Advisory/Consultancy), Astra Zeneca [Research Grant (Institution)], Novartis [Research Grant (Institution)]. C Wang, J Sandhu have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

References


Cite this article as: Wang C, Sandhu J, Fakih M. A case of class 3 MEKI mutated metastatic colorectal cancer with a non-durable tumor marker response to MEK and ERK inhibitors. J Gastrointest Oncol 2019;10(6):1140-1143. doi: 10.21037/jgo.2019.08.02