

Case report

Response to re-challenge of a MEK inhibitor in a patient with recurrent low-grade serous carcinoma of the peritoneum

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ABSTRACT

Low-grade serous carcinoma of the ovary/peritoneum is a rare epithelial cancer subtype characterized by younger age at diagnosis, relative chemoresistance, and prolonged overall survival compared with high-grade serous carcinoma. In addition, alterations in the mitogen activated protein kinase pathway are frequent and play a major role in the pathogenesis of this tumor. MEK inhibitors have demonstrated promising activity in the treatment of recurrent low-grade serous carcinoma. Although prevailing wisdom in cancer therapy is that the re-treatment with a drug after emergence of resistance is futile, we report the initial case of a patient with recurrent low-grade serous carcinoma who experienced a partial response when re-challenged with a MEK inhibitor after previously having prolonged stable disease followed by disease progression on a MEK inhibitor.

1. Introduction

Low-grade serous carcinoma of the ovary/peritoneum (LGSOC) is a rare epithelial cancer subtype first described based on a binary grading system for serous carcinomas in 2004 (Malpica et al., 2004). It is characterized by younger age at diagnosis, relative chemoresistance, and prolonged overall survival compared to high-grade serous carcinoma (Slomovitz et al., 2020). In addition, the mitogen activated protein kinase (MAPK) pathway plays a major role in the pathogenesis of this subtype, with activating mutations of *KRAS*, *BRAF*, *ERBB2*, *NRAS*, and *NFI*, among others (Slomovitz et al., 2020). Because of its relative chemoresistance, a search for more effective therapies for LGSOC has predominated over the past several years. Anti-angiogenic and endocrine therapies have demonstrated promising activity in LGSOC (Slomovitz et al., 2020). Based on the genomic profile of LGSOC, MEK 1/2 inhibition is an attractive strategy for study in this histotype. A phase 2 trial and two subsequent randomized trials of three different MEK inhibitors have revealed efficacy in recurrent LGSOC (Farley et al., 2013; Monk et al., 2020; Gershenson et al., 2019).

Generally, once a patient develops disease progression on a regimen or drug, it is assumed that that patient's tumor has acquired resistance, and re-treatment with the same agent(s) is regarded as futile. Bevacizumab may represent an exception to that rule. We present the first

case of a patient with recurrent LGSOC who responded to re-challenge with a MEK inhibitor following disease progression on treatment with a different MEK inhibitor.

2. Case report

A 25-year-old woman underwent hysterectomy, bilateral salpingo-oophorectomy, appendectomy, and omentectomy in 1987, with findings of a stage III serous borderline tumor, including involvement of bilateral ovaries with serous borderline tumor and non-invasive peritoneal implants in the omentum. She received no further therapy and was placed on estrogen replacement therapy until February 2012, when an enlarged right supraclavicular lymph node was noted, and CT confirmed supraclavicular node enlargement as well as mediastinal lymphadenopathy. Biopsy of the supraclavicular node revealed metastatic LGSOC. Serum CA 125 = 11.1 U/mL. Genomic profiling of this tumor revealed a *KRAS G12D* mutation.

From March 2012 until August 2012, she received 6 cycles of paclitaxel plus carboplatin with some improvement in the size of the supraclavicular node. CT imaging at that point revealed a 2.5 × 3.3 cm right supraclavicular lymph node, calcified anterior diaphragmatic and mediastinal lymphadenopathy (largest node measuring 2.4 × 1.6 cm), and no evidence of peritoneal tumor. In September 2012, she was placed

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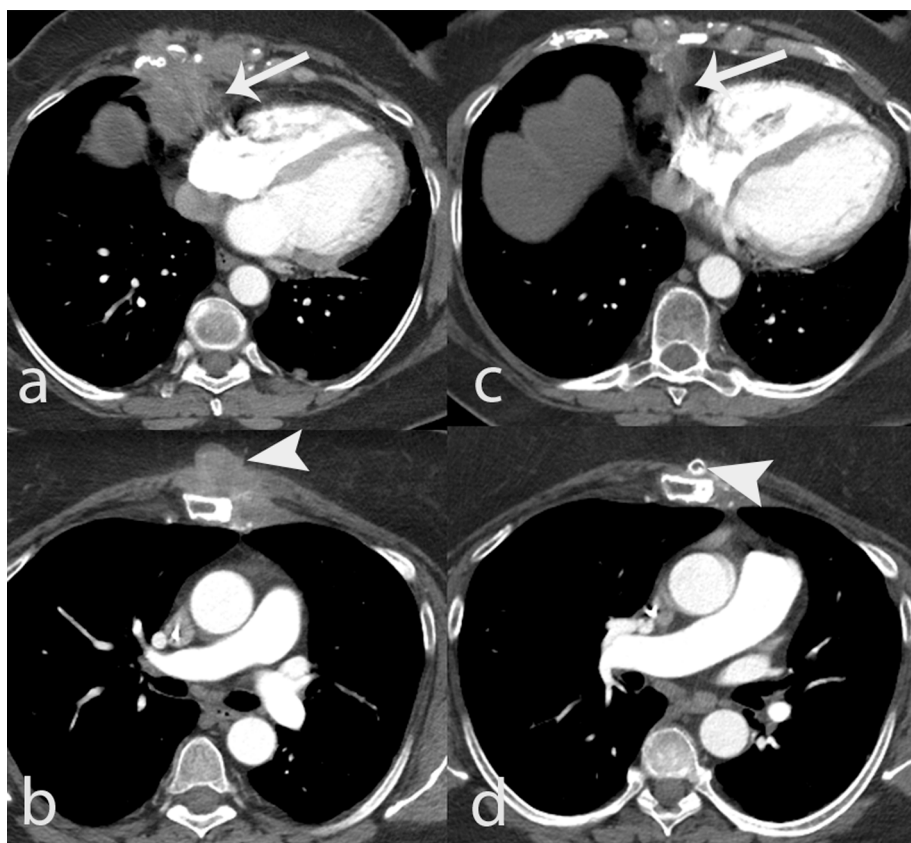


Fig. 1. Pre-treatment axial post contrast images in February 2020 show (a) metastasis in the anterior diaphragmatic region (arrow), and (b) metastasis anterior to the sternum (arrowhead). Post-treatment images in September 2020 show interval significant decrease in size of (c) metastasis in the anterior diaphragmatic region (arrow) and (d) metastasis anterior to the sternum (arrowhead).

on letrozole 2.5 mg daily and received this drug until November 2013, when repeat CT imaging revealed a stable right supraclavicular lymph node but disease progression in the chest.

On January 27, 2014, she enrolled in the MILO/ENGOT-ov11 trial and was randomized to binimetinib 45 mg bid. While on the trial, she experienced grade 3 adverse events of hypertension, increased creatine phosphokinase, and decreased left ventricular ejection fraction, requiring two levels of dose reduction to 15 mg bid for the latter adverse event. The patient had prolonged overall clinical benefit with stable disease for 109 weeks (maximum decrease 25%) until February 24, 2016, when blinded independent central review (BICR) showed disease progression. Subsequently, from April 2016 until February 2020, she received multiple, sequential therapies, including letrozole plus everolimus (stable disease), tamoxifen (progressive disease), pegylated liposomal doxorubicin/carboplatin followed by single-agent pegylated liposomal doxorubicin (partial response), and leuprolide acetate (progressive disease).

On February 2, 2020, the patient was found to have disease progression; CT revealed 2.9 × 1.6 cm right supraclavicular lymphadenopathy, a 3.1 × 2.6 cm left parasternal mass, and 2.5 × 4.1 cm anterior diaphragmatic mass. On February 25, 2020, she started trametinib 2 mg daily. By June 7, 2020, she was noted to have a partial response on CT imaging, with a 41% decrease in measurable disease by RECIST 1.1, and by September 13, 2020, the partial response was confirmed, with a 58% decrease in measurable disease from baseline (Fig. 1). In addition, during this period, serum CA 125 decreased from 22.0 U/mL to 11.4 U/mL. Adverse events on trametinib to date include grade 2 skin rash, diarrhea, and nausea. The patient is continuing trametinib at the time of this report.

3. Discussion

Little is known about the optimal sequencing of therapeutics in the management of recurrent LGSOC. Following primary surgery and adjuvant therapy, options for treatment of relapse include various chemotherapy agents, endocrine therapies, bevacizumab, and targeted agents. MEK inhibitors are oral, non-ATP competitive, small molecule inhibitors of MEK 1/2. To date, they have been FDA approved for treatment of mutation-positive melanoma, mutation-positive non-small cell lung cancer in combination with dabrafenib, and for mutation-positive, advanced or metastatic anaplastic thyroid cancer in combination with dabrafenib.

MEK inhibitors have also demonstrated effectiveness in LGSOC. In the initial phase 2 clinical trial of a MEK inhibitor, selumetinib, in 52 women with recurrent LGSOC, the objective response rate (ORR) was 15%, with another 65% of patients having stable disease, and the median progression-free survival (PFS) was 11.0 months (Farley et al., 2013). However, there was no correlation between the presence of a *KRAS* or *BRAF* mutation and ORR in the 34/52 (65%) of patients with sufficient archival tumor DNA available for mutational analyses. The MILO/ENGOT-ov11 study was a phase 3 randomized trial of binimetinib versus physician's choice chemotherapy (PCC) (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan) in 341 women with recurrent LGSOC (Monk et al., 2020). Although the study was discontinued early based on an interim analysis revealing that the PFS hazard ratio crossed the predefined futility boundary, the updated analysis indicated a median PFS of 10.4 months for binimetinib versus 11.5 months for PCC (HR = 1.15; $p = 0.748$), and an ORR of 24% in both arms of the study. In addition, for patients treated with binimetinib, the ORR and median PFS in the *KRAS* mutant group (ORR = 44%; median PFS = 17.7 months) were significantly better than in the *KRAS* wild-type

group (ORR = 19%; median PFS = 10.8 months) ($p = 0.006$). In the GOG 0281 study, which was a phase 2/3 randomized trial of trametinib versus standard of care (SOC) (physician's choice of one of five drugs—pegylated liposomal doxorubicin, weekly paclitaxel, topotecan, letrozole, or tamoxifen)—260 patients with recurrent LGSOC were enrolled (Gershenson et al., 2019). This trial did meet its primary end point; the median PFS for patients receiving trametinib was 13.0 months versus 7.2 months for SOC (HR = 0.48; $p < 0.001$). The ORR was 26% and 6.2% for trametinib and SOC, respectively ($p < 0.0001$). We also now understand that the molecular biology of some LGSOCs leads to their addiction to the MAPK pathway and exceptional responses to MEK inhibition (Grisham et al., 2015; Takekuma et al., 2016).

Common adverse events associated with MEK inhibitors include skin rash, gastrointestinal symptoms, fatigue, hypertension, and anemia. Uncommon adverse events include pneumonitis, retinal vascular disorders, or cardiac effects, such as left ventricular systolic dysfunction, QTc prolongation, or decreased ejection fraction, the latter of which occurred when our patient was treated with binimetinib.

There are several potential mechanisms for the development of MEK inhibitor resistance. These include reactivation of the MAPK pathway through alterations or mutations in molecules upstream of *ERK* in the MAPK pathway, such as *RAS*, *RAF*, *NF1*, or *MEK*; reactivation of multiple RTKs; or activation of parallel signaling pathways, such as PI3K, STAT3, and Hippo signaling pathways (Kozar et al., 2019; Balmanno et al., 2009; Dai et al., 2011; Mandal et al., 2016). Yet another possible mechanism of resistance involves the ability of tumor cells to switch phenotypes and rewire metabolic pathways (Kemper et al., 2014).

The prevailing concept in cancer therapy is that re-treatment with a drug after emergence of resistance is futile. However, in BRAF-mutated metastatic melanoma, objective responses to re-challenge with combination BRAF inhibitor plus MEK inhibitor following a history of disease progression on combination BRAF/MEK inhibitor therapy have been reported (Valpione et al., 2018). The patient with recurrent LGSOC reported here responded to MEK inhibitor monotherapy following disease progression while receiving a different MEK inhibitor. One explanation is that acquired resistance to targeted therapy may be reversible by some as yet undefined mechanism. Alternatively, it is possible that either the patient's dose reductions of binimetinib to 15 mg bid (due to decreased ejection fraction) prevented the drug from achieving sufficient dose intensity, thus leading to disease progression, or trametinib is actually more effective than binimetinib in the treatment of recurrent LGSOC. Fernandez et al. conducted a study of four different MEK inhibitors—trametinib, selumetinib, binimetinib, and refametinib—in LGSOC patient-derived cell lines (Fernandez et al., 2016). A single dose of trametinib was found to have a greater influence on cellular proliferation than ten-fold higher doses of the other three MEK inhibitors.

In summary, based on this initial report of response to re-challenge of a MEK inhibitor in a patient who previously demonstrated disease progression on a MEK inhibitor, this treatment strategy is recommended for further consideration. Although the example presented involves re-challenge with a MEK inhibitor different than the initial drug, re-challenge with the same MEK inhibitor is worthy of attention as well.

Importantly, outside a clinical trial, trametinib is currently the only MEK inhibitor listed on the NCCN compendium as a treatment option for recurrent LGSOC, which will restrict MEK inhibitor options for re-treatment. With greater experience, we will learn if this case represents the exception or is more typical.

CRediT authorship contribution statement

David M. Gershenson: Conceptualization, Writing - original draft, Writing - review & editing, Data curation. **Priya Bhosale:** Data curation, Writing - review & editing. **Rachel N. Grisham:** Data curation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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