Short Communication

Response to MEK inhibitor in small cell neuroendocrine carcinoma of the cervix with a KRAS mutation

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Introduction

Small cell neuroendocrine carcinoma (SCNEC) of the cervix is a rare and aggressive form of cervical cancer. Compared with squamous cell or adenocarcinoma of the cervix, SCNEC is more likely to have lymph node metastases, lymphovascular invasion, recurrence, and overall poorer prognosis [1]. Neuroendocrine tumors can recur both locally and distantly within months after complete surgical resection with no residual disease [2].

Molecular targeted therapy has been shown to have variable results in non-gynecologic neuroendocrine tumors including small cell carcinoma of the lung, gastrointestinal stromal tumors (GIST) and pheochromocytomas. C-kit is a growth factor receptor that contains tyrosine kinase domains and is frequently mutated in GIST [3]. Imatinib is an ATP analogue that has been shown to inhibit growth and proliferation of GIST which frequently has c-kit mutations. Both partial and complete responses have been observed in patients with GIST [3].

The RAS pathway is frequently targeted by mutations in human cancers, which leads to deregulation of the pathway. One of the most studied pathways is the RAF-mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) kinase (MEK) MAPK cascade [4]. This pathway is involved in various key activities including angiogenesis, apoptosis, and proliferation. Therapeutic agents have been designed to inhibit the downstream components of this pathway, including RAF and MEK inhibitors.

The MEK inhibitor, trametinib, is FDA-approved for treatment of unresectable or metastatic melanoma in patients with BRAF mutations. There is also activity in KRAS mutations as both lead to activation of the MAPK pathway. We report a case of treatment response to an MEK inhibitor in a patient with recurrent neuroendocrine carcinoma of the cervix after molecular testing identified a KRAS mutation.

Case

A 52-year-old Caucasian female experienced postmenopausal bleeding and was noted to have endometrial cells on her pap smear. She underwent colposcopy, endometrial biopsy, and cervical biopsy as part of the work-up. Final pathology of the cervical biopsy revealed high-grade neuroendocrine carcinoma with mixed small cell and large cell types. PET/CT was negative for metastatic disease. Clinical stage was determined as IB1.

The primary treatment was robotic-assisted radical hysterectomy, bilateral salpingoophorectomy, and bilateral pelvic lymph node dissection. The margins of the tumor were negative and the lymph nodes did not show any evidence of metastasis. Due to her high risk histology, the patient underwent adjuvant chemo-radiotherapy for a total of 4500 cGy in 25 fractions concurrent with weekly cisplatin. After completion of radiation she received an additional 4 cycles of adjuvant cisplatin and etoposide chemotherapy. At the conclusion of primary treatment the patient was without evidence of disease both on physical exam and CT scan of the chest, abdomen, and pelvis.

Approximately 4 months later, the patient was examined during a surveillance visit and a 3 mm friable lesion was noted at the apex of the right vaginal cuff. Biopsy confirmed recurrence of the neuroendocrine carcinoma. PET/CT revealed disease limited to the vagina. Prior to this, the tissue specimen from surgery was tested for molecular genetics through an institutional testing program where a panel of 46 genes commonly associated with cancer is tested through next generation sequencing. The patient was noted to have a KRAS mutation detected in codon 12, exon 2 (GTT to GAT) of the KRAS gene that would change the encoded amino acid from Glycine to Aspartate (p.Gly12Asp).

Standardized nomenclature for this mutation is NM_033360.2 (KRAS): c.35G>A p.G12D. No other genetic mutations were detected. She was therefore started on an MEK inhibitor, trametinib off trial as there were no MEK trials available at that time. The patient has undergone...
8 cycles of the MEK inhibitor, each 4 weeks long, and is currently without evidence of disease as confirmed by PET/CT.

The patient continues to maintain an excellent quality of life and has an Eastern Cooperative Oncology Group (ECOG) performance status of 0. Her only long-term treatment complication is chronic lymphedema for which she receives massage therapy. She has been seen by ophthalmology secondary to visual disturbances after starting trametinib and she was diagnosed with dry-eye and given hydrating eye drops.

Discussion

The current treatment of SCNEC of the cervix is extrapolated from treatment for small cell carcinoma of the lung which involves a combination of surgery, chemotherapy, and/or radiation [5]. FIGO stage and lymph node metastases have been proposed as significant prognostic factors in SCNEC of the cervix in one of the largest retrospective studies to date [5]. Unfortunately, most patients with SCNEC will develop recurrent disease. Recurrence of SCNEC of the cervix has been shown to occur more frequently in women who did not receive initial systemic treatment with chemotherapy [6]. Distant metastases are found more commonly in the liver, bone, lung, and brain when compared to metastases in squamous cell carcinoma of the cervix which more commonly occur in the pelvis and lymph nodes.

Lee et al. compared rates of recurrence and survival between SCNEC and squamous cell carcinoma of the cervix. They found that approximately 60% of patients with SCNEC recurred and the 5-year overall survival was 23.5% for SCNEC compared to 87.9% for the squamous cell carcinoma group [7]. Given the extremely poor prognosis of SCNEC of the cervix, treatment options for recurrent disease are of great importance. This is especially true since multi-modality treatment is being used upfront in patients with early-stage SCNEC. After recurrence, new treatment options are limited to second-line chemotherapy and experimental treatments.

Targeted therapy for oncogenic mutations is an expanding field with promising new options for patients with refractory disease. KRAS mutations were found to have a prevalence of approximately 9% in a study by Wright et al. that examined oncogenic mutations in squamous and adenocarcinomas of the cervix [8]. KRAS mutations were only found in those patients with adenocarcinoma, with no mutations present in squamous cell carcinoma [8]. No change in survival was observed in patients with KRAS mutation [8]. These findings, although not specific for SCNEC of the cervix, demonstrate the potential of targeted therapy for treatment of carcinoma of the cervix.

To our knowledge this is one of the first reports of successful treatment of recurrent SCNEC of the cervix using a MEK inhibitor. Current literature using MEK inhibitors has been demonstrated for melanoma, non-small-cell lung cancer, breast, colon, and pancreatic cancer. MEK inhibitors are approved treatment for advanced melanoma, but have not been shown to improve disease in breast, non-small-cell lung, breast, colon, and pancreatic cancer [9]. At MD Anderson, we have performed molecular testing in 20 women with small cell neuroendocrine cervical cancer and found 13 different mutations in 15 (75%) of these patients (5 tumor specimens had >1 mutation). The two most common mutations seen were RAS (n = 4) and p53 (n = 4). (manuscript submitted for publication).

In this case, trametinib was used for recurrent SCNEC of the cervix in a patient with a known KRAS mutation. The patient has been on trametinib for 8 cycles now and is without evidence of disease. The role of molecular testing to determine response to targeted therapies is ongoing. This is particularly challenging in patients with rare tumors where clinical trials are less available. This case highlights the potential benefits of molecular testing to determine treatment in a patient with a rare but aggressive tumor, where conventional therapy has limitations.

Conflict of interest

There are no conflicts.

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