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Case report

Ipilimumab and nivolumab for recurrent neuroendocrine cervical carcinoma

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ABSTRACT

Neuroendocrine carcinoma of the cervix is a rare subtype of cervical cancer with a poor prognosis. Primary treatment of this disease involves a combination of surgery, chemotherapy, and radiation. The majority of patients will experience disease recurrence, for which there exist no treatment guidelines. Because of histologic similarities, small cell lung cancer has often informed management of extrapulmonary neuroendocrine carcinomas. Immunotherapy regimens, including a combination of ipilimumab and nivolumab, have been shown to have activity in small cell lung cancer. In this report, we present the cases of 3 patients with recurrent neuroendocrine carcinoma of the cervix who experienced durable response to a combination of ipilimumab and nivolumab.

1. Background

Neuroendocrine carcinoma of the cervix (NECC) is a rare, aggressive subset of cervical cancer. Historically categorized into four histologic subtypes (typical carcinoid, atypical carcinoid, small cell, and large cell), neuroendocrine tumors are now classified by the World Health Organization as either low-grade neuroendocrine tumor or high-grade neuroendocrine carcinoma (NEC), eschewing the carcinoid terminology. Within this terminology system, NEC is subdivided into small cell, large cell, and mixed. (Winer et al., 2021)

NECC accounts for 1–5% of all cervical cancers and typically affects young women. (Tempfer et al., 2018) Small cell NECC is the most common, comprising 80% of cases. (Tempfer et al., 2018) NECC is an aggressive disease with early and erratic hematologic and lymphatic spread. Prognosis is poor, with a 5-year overall survival of approximately 34%, though this is dependent on stage. (Tempfer et al., 2018) A recent analysis found 5-year survival rates of 64.5%, 50.1%, 30.2%, and 3.4% for Stage I, II, III, and IV disease, respectively. (Ishikawa et al., 2019) Owing to the rarity of NECC, there are no consensus guidelines for management. A combination of platinum-based chemotherapy and etoposide with radiation therapy appears to offer improved survival over other approaches and has become the *de facto* standard treatment. (Hoskins et al., 2003)

Approximately 65% of NECC cases recur. (Zivanovic et al., 2009) In this setting, a regimen of topotecan, paclitaxel, and bevacizumab was reported to induce a more favorable progression-free survival compared with other regimens, though it is highly toxic. (Frumovitz et al., 2017) Data are limited for third-line chemotherapy. Owing to their histologic similarities, small cell lung cancer (SCLC) informs treatment of NECC. A combination of the PD-L1 antibody nivolumab and the CTLA4 antibody ipilimumab has been found to induce an overall response rate of 20% in SCLC. (Antonia et al., 2016) We have treated 3 patients with recurrent NECC with ipilimumab/nivolumab and describe our experience here. Table 1 summarizes pertinent tumor characteristics, including PD-L1 expression, tumor mutation burden, microsatellite stability status, as well as treatment history for each patient.

2. Cases

Patient 1 was diagnosed with small cell NECC in her late 20 s. She received 6 cycles of cisplatin/etoposide with radiation therapy with partial disease response. At recurrence, she received topotecan, paclitaxel, and bevacizumab for 6 cycles. Ipilimumab/nivolumab was initiated at progression of disease. After 6 cycles, PET CT showed near

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complete disease response. At the time of this report, the patient is completing cycle 14 of this regimen with maintained response (83 weeks with stable disease).

Patient 2 underwent radical hysterectomy in her mid-40s for suspected squamous carcinoma confined to the cervix. She experienced a vaginal cuff recurrence 4 months later; biopsy of the lesion was favored to be large cell NECC, prompting re-evaluation of the initial pathology, which was determined to be large cell NECC. PET CT demonstrated multiple hypermetabolic pelvic and abdominal wall lesions, consistent with metastatic recurrence. She received 3 cycles of cisplatin/etoposide, after which she was found to have progression of disease. The patient was transitioned to ipilimumab/nivolumab with concurrent external beam radiation therapy to the pelvis. Imaging showed gradual disease response. She was found to progress after cycle 10 (progression-free survival = 53 weeks).

Patient 3 underwent a cervical LEEP for CIN 2 in her early 40 s; final pathology revealed large-cell NECC confined to the cervix. She underwent radical hysterectomy, followed by 6 cycles of cisplatin/etoposide. Five years later, she was found to have a pelvic mass on surveillance CT. PET CT was ordered, as proximity to vasculature precluded biopsy of the mass, and demonstrated hypermetabolic activity within the pelvic mass, as well as hypermetabolic liver lesions, confirming metastatic recurrence. She was treated again with cisplatin/etoposide. Due to persistent disease, this was followed by 6 cycles of bevacizumab, then 3 months of daily everolimus. She was thereafter started on ipilimumab/nivolumab with concurrent radiation to abdominal lymph nodes. One year later, she developed progression of (progression-free survival = 53 weeks).

3. Discussion

NEC was originally thought to arise from amine-precursor uptake and decarboxylase (APUD) cells within the extrapulmonary neuroendocrine system. However, several older studies of extrapulmonary malignancies with mixed neuroendocrine/non-neuroendocrine histology detected identical mutations within the neuroendocrine and non-neuroendocrine carcinoma components. (Frazier et al., 2007; Rossi et al., 2004; Hoang et al., 2001) As a result, NEC is now suspected to originate from pluripotent stem cells. (Frazier et al., 2007) Because NECC are histologically identical to extracervical NEC, they have historically been equated. However, a recent analysis found NECC to be more genomically similar to non-neuroendocrine cervical carcinomas, rather than extracervical NEC. (Hillman et al., 2020) Additionally, the human papillomavirus (HPV), a causative agent in the development of squamous cell and adenocarcinoma of the cervix, is detectable in approximately 85% of small cell NECC and 88% of large cell NECC. (Castle et al., 2018; Alejo et al., 2018) A similar examination of small cell lung cancer did not identify a link to high-risk HPV infection. (Hartley et al., 2015) These data support the notions that NEC arise from a precursor cell capable of both neuroendocrine and non-neuroendocrine differentiation and that NECC may be more closely related to non-neuroendocrine cervical carcinoma than has been previously supposed.

A combination immunotherapy regimen in the form of ipilimumab/nivolumab, previously demonstrated in clinical trials to have activity in SCLC, has been reported in case studies to effect response in an instance of HPV-mediated oropharyngeal cancer. (Ho et al., 2018) Data on the combination of ipilimumab/nivolumab for recurrent NECC is limited to single digit numbers, found in a combination of clinical trials and case studies. Recently, Paterniti *et al.* reported a single case of complete response to the drug combination in a patient with NECC. (Paterniti et al., 2021) The DART trial, a phase II basket trial examining the use of ipilimumab/nivolumab for rare tumor types, published an analysis of the study's high-grade neuroendocrine cohort, which included two NECC. This analysis calculated an overall objective response rate of 22%, with responses seen in poorly differentiated pancreatic, rectal, colon, esophageal, and lung tumors. Of the two patients in the cohort with NECC, one patient had a nearly 30% reduction in tumor measurement, while the other had a just-under 50% increase. (Patel et al., 2021) A separate analysis of all nonpancreatic NEC treated in the DART trial included 3 NECC cases; of these, one patient had a partial response. (Patel et al., 2020) More recently, a retrospective analysis of NEC treated with ipilimumab/nivolumab, which included 1 case of NECC, found an overall objective response rate of 14.7%. (Al-Toubah et al., 2021)

These reports and our experience suggest some patients with NECC will have robust and durable responses to this drug regimen, even in those whose tumors does not express PD-L1. Given the dearth of effective management options for such patients, consideration can be given to employing ipilimumab/nivolumab in the treatment of patients with recurrent NECC.

4. Consent

All patients provided consent for their health information to be disclosed to researchers for research purposes. Our Institutional Review Board does not consider case reports to be human research and thus does not require patient consent for publication of such health information. All potentially identifying information has been removed from the patient case descriptions.

CRediT authorship contribution statement

Mary Towner: Conceptualization, Data curation, Writing. **Karen Novak:** Data curation. **Young Kwang Chae:** Data curation. **Daniela Matei:** Data curation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: YKC has received grants from Abbvie, BMS, Biodesix, Lexent Bio, and Freenome and consulting fees and/or honoraria from Roche/Genentech, AstraZeneca, Foundation Medicine, Counsyl, Neogenomics, Guardant Health, Boehringer Ingelheim, Biodesix, Immuneoncia, Lilly Oncology,

Table 1
Characteristics of three patients receiving ipilimumab/nivolumab for recurrent neuroendocrine carcinoma of the cervix.

Histologic subtype	PD-L1 expression[δ]	MSI status	TMB (mut/MB)	Prior radiation	Prior systemic treatment	Progression-free survival after ipilimumab/nivolumab (weeks)
Small cell	≥1%	Stable	2.6	Yes	1. Cisplatin/ etoposide 2. Topotecan/ paclitaxel/ bevacizumab	Treatment ongoing; currently 83 weeks with stable disease
Large cell	≥1%	Stable	9	No	1. Cisplatin/ etoposide	53
Large cell	0%	Stable	12.44	Yes	1. Cisplatin/ etoposide 2. Bevacizumab 3. Everolimus	53

MSI = microsatellite instability; TMB = tumor mutation burden.
[δ] Percentage of all PD-L1 positive cells divided by the number of viable tumor cells.

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