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PARP and PD-L1 as Potential Therapeutic Targets for Women with Neuroendocrine Cervical Cancer

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Abstract

Objectives: Women with recurrent neuroendocrine cervical cancer have few effective treatment options. The aim of this study was to identify potential therapeutic targets for women with this disease.

Methods: Specimens from patients with neuroendocrine carcinomas of the cervix were identified from pathology files at M.D. Anderson Cancer Center. Immunohistochemical stains for PD-L1 (DAKO, clone 22-C3), mismatch repair proteins (MLH1, MSH2, MSH6, PMS2), somatostatin, and Poly (ADP-ribose) polymerase (PARP) were performed on sections from formalin-fixed paraffin-embedded tissue blocks. Nuclear PARP-1 staining was quantified using the H-score with a score of <40 considered low, 40-100 moderate, and ≥100 as high

Results: Forty pathologic specimens from patients with neuroendocrine carcinomas of the cervix were examined (23 small cell, 5 large cell, 3 undifferentiated neuroendocrine, and 9mixed). The mean age of the cohort was 43.0 and the majority patients (70%) identified as white, non-Hispanic. All 28 (100%) samples tested stained for mismatch repair proteins demonstrated

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Author Contributions:

Dr. Carroll analyzed data and drafted the manuscript. Dr. Ramalingam was involved in study design, data collection, analysis, and manuscript review. Drs. Fujimoto, Salvo, Solis Soto, Phoolchaoren, Hillman and Cardnell were involved with data collection, analysis, and manuscript review. Dr. Byers and Dr. Frumovitz were responsible for data collection, analysis, study design, and manuscript review. All authors had approval of the final version of the manuscript.

Competing Interests: Dr. Byers has served as a consultant for Medivation, Inc, AbbVie, BioMarin Pharmaceutical Inc., Lilly Humana, LUNGevity. She has served on Scientific Advisory Committee's for AstraZeneca Pharmaceuticals, StemCentrx, Astex Therapeutics, GENMAB. Dr. Frumovitz has served as a consultant for Stryker, Genetench, and Ipsen.

intact expression suggesting they are microsatellite stable tumors. In the samples tested for PD-L1 expression, only 1 (5%) of the 22 pure small cell specimens tested positive whereas 3 (50%) of the 6 mixed specimens tested positive. In addition only 1 (33%) of 3 undifferentiated neuroendocrine carcinomas were PD-L1 positive. Of the 11 small cell specimens tested for PARP-1, 10 (91%) showed PARP expression with 6 (55%) demonstrating high expression and 4 (36%) showing moderate expression. Somatostatin staining was negative in 18 of 19 small cell cases (95%).

Conclusions: Single agent PD-L1 inhibitors are unlikely to be effective in pure high grade neuroendocrine cervical carcinomas as all tumors tested were microsatellite stable and overwhelmingly negative for PD-L1 expression. As the majority of tumors tested expressed PARP-1, inclusion of PARP inhibitors in future clinical trials may be considered.

Keywords

cervical cancer; neuroendocrine; immunotherapy; biomarkers; small cell cervical cancer

Introduction

Small and large cell cervical cancers are rare types of high-grade neuroendocrine malignancies that are histologically similar to small cell lung cancer.[1] There are multiple sites of origin for extra-pulmonary small cell neuroendocrine cancers including cervix, uterus, gastrointestinal tract, head, neck, and genitourinary tract.[2] High grade neuroendocrine carcinomas from all sites share an aggressive natural history with widespread disease common at diagnosis and, even in local disease, a high risk for recurrence.[2,3] The Society of Gynecologic Oncology guidelines recommend a multimodal treatment approach to newly diagnosed neuroendocrine cervical cancer, combining experience with adenocarcinoma and squamous cell carcinomas of the cervix with small cell carcinoma of the lung with a role for platinum based chemotherapy, radical surgery, and/or radiation depending on stage.[4]

For recurrent high grade neuroendocrine cervical cancer, there remains no standard therapeutic options and survival is poor.[5] Chemotherapy with topotecan, paclitaxel, and bevacizumab has shown some promise in improving outcomes for women with this disease however better therapeutic options for recurrent disease are needed.[5,6] Multiple targeted agents and immunotherapies have shown activity in other high grade neuroendocrine tumors but their utility in cervical tumors has not been extensively evaluated.

Pembrolizumab, an anti-PD-1 antibody, has improved response rates in tumors from multiple sites that harbor significant mutational burden in mismatch-repair genes (MLH1, MSH2, MSH6, PMS2) as well as in PD-L1 positive disease.[7,8] The FDA has recently approved pembrolizumab for recurrent or metastatic cervical cancer that test positive for PD-L1. In addition, pembrolizumab has been approved for the treatment of recurrent small cell lung cancer. Another drug commonly used to treat recurrent gastrointestinal neuroendocrine tumors is somatostatin. The somatostatin receptor (SST) has been an effective target for neuroendocrine and carcinoid tumors and small cell cervical cancer have previously been shown to be positive for the somatostatin receptors.[9,10] Finally, neuroendocrine tumors from multiple different sites have shown potential sensitivity to PARP inhibitors. Molecular

studies in recurrent neuroendocrine carcinomas of the prostate and lung have shown overexpression of PARP and inhibition of tumor growth with PARP inhibitors.[11,12]

Effective treatment options for recurrent neuroendocrine cervical cancer remains an unmet need. Small cell cancers from extra-cervical sites have successfully identified active treatment regimens utilizing pathologic immunohistochemistry. The goal of this study was to utilize immunohistochemistry to identify immune and molecular targets for potential therapeutic strategies in the treatment of recurrent small cell cervical cancer.

Methods

Slides and formalin fixed paraffin embedded tumor blocks from either biopsies or resection specimens of 40 cervical neuroendocrine carcinomas were identified from the pathology files between 2004-2016. This study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center. Clinical data from these patients were obtained from medical records including demographics such as age, race, body mass index, and stage of disease at diagnosis.

Immunohistochemical stains were performed with specific antibody staining of treated paraffin embedded tissue samples. Samples were first placed in the oven for 30 minutes before being loaded into the stainer for all markers except PD-L1. For PD-L1 staining, samples were first placed in the oven for 60 minutes before being loaded into the PT. Antigen epitopes were unmasked by heat induced epitope retrieval (HIER). Endogenous peroxidases were neutralized with hydrogen peroxide. Samples were then challenged with specific antibodies to the proteins of interest. Prior to secondary antibody challenge blocking the samples were bathed in blocking serum. Secondary biotin-conjugated antibodies were then added and reaction with diaminobenzidine tetrachloride was observed.

Separate stains were done for each of the following: for mismatch repair proteins (MLH1 Clone G168-728, Cell Marque), MSH2 (Clone FE11, Calbiochem), MSH6 (Clone 44, BD Biosciences), PMS2 (Clone A16-4, BD Biosciences), PD-L1 (DAKO, clone 22-C3), somatostatin (EP130 Cell Marque), and Poly (ADP-ribose) polymerase (PARP) were performed on sections from these tissue blocks. Staining for mismatch repair proteins (n=28) was interpreted as either positive or negative, in the presence of positive internal controls. PD-L1 (n=31) was interpreted as positive (CPS>1) when there was either partial or complete membrane staining in the tumor cells. Percentage of staining was also estimated. Somatostatin staining (n=19) was cytoplasmic, and both percentage and intensity of staining were evaluated. Nuclear PARP-1 (n=11) staining was quantified using the H-score with a score of <40 considered low, 40-100 moderate, and ≥100 as high.[13]

Results

Demographic and stage data are summarized in Table 1. The 9 patients with mixed histologies had components of both high grade neuroendocrine and squamous, adenocarcinoma or, adenosquamous carcinoma. All of the 28 specimens tested demonstrated intact mismatch repair protein expression for each of the four proteins tested (MLH1, MSH2, MSH6, PMS2). (Table 2) Thirty-one specimens were tested for PD-L1. Of these,

only 1 (5%) of the 22 pure small cell specimens tested positive whereas 3 (50%) of the 6 mixed specimens tested positive. In addition 1 (33%) of 3 undifferentiated neuroendocrine carcinomas were PD-L1 positive.

Somatostatin staining was positive in 1 (5%) out of 19 small cell samples and demonstrated only moderate staining. A total of 11 small cell specimens were tested for PARP-1 and 91% (n=10) tested positive with 55% (n=6) of positive samples were positive demonstrating high expression and 36% (n=4) showing moderate expression.

Discussion

The results of the immunohistochemistry staining of these high-grade neuroendocrine cervical cancer specimens present potential therapeutic approaches for treating recurrent disease. Unlike well- and moderately-differentiated neuroendocrine tumors of the gastrointestinal system, high-grade neuroendocrine cervical cancers specimens do not express the somatostatin receptor and therefore are unlikely to respond to somatostatin analogues. In addition, neuroendocrine cervical cancer tumors are microsatellite stable without significant expression of PD-L1 raising concerns for potential lack of activity with PD-1/PD-L1 inhibitors. In contrast, significant PARP expression was noted in an overwhelming majority of the samples tested. Therefore, there may be good rationale for utilizing PARP inhibitors as part of potential therapeutic approaches for treating women with this disease.

Immunohistochemistry testing of tissue samples for mismatch repair proteins (MLH1, MSH2, MSH6, PMS2) has an excellent predictive value for diagnosing microsatellite instability (MSI), although up to 11% of MSI tumors are not detected using these markers.[14] While unlikely, there is a small possibility that our methods missed some MSI positive tumors.[15,16] MMR deficient tumors have been shown to overexpress PD-1 suggesting a population of tumors susceptive to immune checkpoint blockade and our lack of PD-1 expression supports the notion that these tumors are MMR intact.[17] This was demonstrated in various microsatellite unstable tumors that PD-1 blockade with an anti-PD-1 antibody, pembrolizumab, led to partial disease response in over 50% of patients, with complete response in 21%.[7]

The FDA recently approved pembrolizumab in recurrent cervical cancer that is PD-L1 positive based on the results from the KEYNOTE-158 study.[18] In that study, however, women with cervical cancers that were PD-L1 negative (CPS score < 1) saw no response to single agent pembrolizumab. As this current study shows most patients with high grade neuroendocrine cervical carcinomas will be PD-L1 negative on immunohistochemistry, some might hypothesize that single agent pembrolizumab will be unlikely to have significant activity in these patients. To that end, in a recent phase II basket trial of pembrolizumab in rare tumors, there were no responses in 7 women with small cell neuroendocrine carcinoma of the lower genital tract.[19]

In the KEYNOTE-158 study all patients in the cervical cancer cohort had squamous, adeno-, or adenosquamous carcinomas and 84% tested positive for PD-L1 on

immunohistochemistry. There were no patients with high-grade neuroendocrine carcinoma of the cervix.[18] In our study, only 1 (5%) of 22 patients with pure small cell histology tested positive for PD-L1. However, 3 (50%) of 6 patients with mixed histology tested positive, likely due to the squamous or adenocarcinoma components of the mixed tumor.

Published guidelines recommend that clinicians apply strategies for treating small cell lung cancer to patients with high-grade neuroendocrine cervical cancers.[4] While tumor PD-L1 expression is the single factor most correlated with response to therapy, data from Checkmate-032 supports nivolumab as an active agent in small cell lung cancer despite lack of PD-L1 expression.[20,21] There has been at least one report of a woman with PD-L1 negative small cell cervical cancer responding to single agent nivolumab.[22] This supports the theory that there may still be a role for these agents in the treatment of recurrent small cell cervical cancer. Other factors in the tumor microenvironment, including tumor mutational burden and neoantigen expression seem to play just as important a role in predicting efficacy of these agents.[23-25] Combination of anti-PD-1 therapy with other agents as ionizing radiation and DNA damage-inducing chemotherapeutics may upregulate PD-L1 expression which in turn may then offer an opportunity for immunotherapies in high-grade neuroendocrine tumors.[26]

The most promising results in this study may be the high expression of PARP in almost all the samples with many of them having high expression. Comparison of small cell and non-small cell lung cancers have demonstrated high PARP expression in small cell lung cancer cells and in that study small cell lung cancer cell lines also had high sensitivity to PARP inhibitors.[13] Homologous recombination deficiency (HRD) was not tested in our samples, while this is known to be a predictive biomarker for PARP inhibitor efficacy in platinum sensitive ovarian cancer, in the ARIEL3 trial the authors noted some BRCA2 wild-type patients and low loss of heterozygosity patients had clinical benefit with rucaparib.[27] The ARIEL3 data supports the findings of ENGOT-OV16/NOVA that PARPi therapy can be beneficial without known HRD.[28] Other biomarkers for PARP inhibitor efficacy, such as the helicase SLFN11, have also been shown *in vivo* to correlate with tumor sensitivity to PARP inhibitors.[29] In a recent randomized phase II study in small cell lung cancer, patients with tumors expressing SLFN11 had improved survival with the combination of temozolomide, an alkylating agent, and the PARP inhibitor veliparib compared to those who did not express SLFN11.[30] In this study, we did not stain for SLFN11, but hope to do so in future projects.

PARP-1 has been shown not only to have a role in DNA repair, but also in DNA methylation as well as having an effect on transcription factors.[31] Jiao et al. found that treatment with PARP inhibitors led to increased PD-L1 expression in breast cancer cell lines and xenograft tumors.[32] The combination PD-L1 blockers and PARP inhibitors in these models worked synergistically improving efficacy over either therapeutic alone. Similarly, Sen et al. showed that PARP inhibition significantly potentiates the effectiveness of PD-L1 inhibitors in small cell lung cancer cell lines and the combination produced complete responses in mouse models.[33] This suggests that while the small cell cervical cancer samples we tested do not currently express PD-L1 or demonstrate microsatellite instability, PARP inhibitions may

induce expression of PD-L1 creating an opportunity for the use of PD-1/PD-L1 inhibitors in combination with PARP inhibitors in this disease.

Our data are limited in that it is only *in vitro* however with the advantage of using patient samples rather than derived cell lines. We are also limited in the number of patients available to study, however for such a rare disease our sample size is a robust sample. Despite numerous ongoing studies of extra pulmonary small cell cancer we believe this is the first to evaluate potential targets at the cervix. This immunohistochemistry profile can help inform research avenues into new therapeutic options in recurrent neuroendocrine cervical cancer. It would be interesting to see if the dynamic changes seen in small cell lung cancer could be replicated in neuroendocrine cervical cancer.

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Table 1.

Demographics

Age, mean, y	43
Body Mass index, mean, kg/m^2	27
Race/ethnicity, n (%)	
White	28(70)
Black	2(5)
Hispanic	3(8)
Asian	5(13)
Unknown	2(5)
Stage at diagnosis, n (%)	
IB1	14(38)
IB2	6(16)
IIA	3(9)
IIB	4(11)
IBB	3(8)
IIIC1	1(3)
IV	6(16)
Unknown	3
Histology, n (%)	
Small Cell Carcinoma	23(58)
Large Cell Carcinoma	5(13)
Mixed	9(23)
High Grade	3(8)

Table 2.

Biomarker Staining

Biomarker	n (%)
MMR, all subtypes	
Intact	28(100)
Deficient	0
PD-L1	
Small Cell	
Positive	1(5)
Negative	21(95)
Undifferentiated	
Positive	1(33%)
Negative	2(66%)
Mixed	
Positive	3(50%)
Negative	3(50%)
SST, small cell	
Positive	1(5)
Negative	18(95)
PARP-1, small cell	
High	6(55)
Moderate	4(36)
Low	0
Negative	1(9)

MMR, Mismatch Repair; SST, Somatostatin; PD-L1, Programmed death-ligand 1; PARP-1, Poly-(ADP-Ribose) Polymerase 1. H-score ≥100 is High and H-score 40-100 is Moderate.