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Sequencing of mutational hotspots in cancer-related genes in small cell neuroendocrine cervical cancer

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HIGHLIGHTS

- Hotspot mutations were found in 55% of patients with small cell cervical cancer.
- Druggable mutations were seen in 48% of patients with small cell cervical cancer.
- PIK3CA (18%), KRAS (14%), and TP53 (11%) were the most common mutations present.

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ABSTRACT

Objectives. Small cell cervical cancer is a rare malignancy with limited treatment options for recurrent disease. We sought to determine if tumor specimens of small cell cervical cancer harbor common somatic mutations and if any of these are actionable.

Methods. Using a registry of patients with neuroendocrine cervical cancer, we identified 44 patients with pure or mixed small cell cervical cancer who had undergone mutational analysis. Mutations had been detected using next generation sequencing of mutational hotspots in 50 cancer-related genes.

Results. Thirty-five mutations were identified in 24 patients (55%). Fifteen of these 24 patients (63%) had 1 mutation, 7 patients (29%) had 2 mutations, and 2 patients (8%) had 3 mutations. In all 44 patients, the most commonly seen mutations were mutations in *PIK3CA* (8 patients; 18%), *KRAS* (6 patients; 14%), and *TP53* (5 patients; 11%). No other mutation was found in >7% of specimens. Of the 24 patients who had a mutation, 21 (88%) had at least 1 alteration for which there currently exists a class of biological agents targeting that mutation. In the entire cohort of 44 patients, 48% had at least 1 actionable mutation.

Conclusion. Although no single mutation was found in the majority of patients with small cell cervical cancer, almost half had at least 1 actionable mutation. As treatment options for patients with recurrent small cell cervical cancer are currently very limited, molecular testing for targetable mutations, which may suggest potential therapeutic strategies, may be useful for clinicians and patients.

1. Introduction

Although the incidence of cervical cancer has steadily decreased in developed countries because of effective screening and human papillomavirus (HPV) vaccination, cervical cancer remains the second most prevalent cancer among women worldwide [1]. The vast majority (>95%) of cervical cancers are of the HPV-associated histologic subtypes of squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma [2]. Fewer than 1% of women with cervical cancer have a neuroendocrine tumor, which translates to approximately 100 to 200 cases of neuroendocrine cervical cancer diagnosed each year in the United States.

Neuroendocrine carcinoma of the cervix encompasses several histologic subtypes, including small cell, large cell, and carcinoid (low- and high-grade) tumors. Unlike the more common squamous and adenocarcinoma subtypes, which spread primarily by local extension, small and large cell neuroendocrine cervical cancers have a propensity to spread both locally and hematogenously, and affected patients frequently present with extrapelvic disease (e.g., liver and lung parenchymal metastases) at initial diagnosis [3]. In addition, even among patients with disease clinically limited to the cervix, the prevalence of regional nodal disease is substantially higher among patients with

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neuroendocrine cervical cancer than among patient with the more common histologic subtypes: up to 40% of newly diagnosed patients with stage IB1 small cell cervical cancer have nodal metastases [3–5]. Stage for stage, the survival of women with small cell carcinoma of the cervix compares poorly against the survival of women with the more common cervical cancer subtypes.

Because of the rarity of small cell carcinoma of the cervix, no prospective trials have been performed to determine optimal therapy for women with the disease. These tumors do, however, have pathologic appearances and clinical behaviors similar to those of small cell lung cancer. Therefore, almost all patients with small cell cervical cancer receive cisplatin and etoposide as part of their primary therapy, according to guidelines developed by professional societies and largely extrapolated from treatment protocols for small cell lung cancer [6,7]. In addition, because of the aggressiveness of small cell cervical cancer, most patients undergo multimodal therapy with consideration of surgery, radiation therapy, and/or chemotherapy. Fifty-eight percent of patients receive dual-modality treatment, and 9% receive all 3 treatment modalities [8]. Nevertheless, overall survival remains poor, despite multimodal treatment plans, with 5-year survival rates ranging from 13% to 25% for all patients and as low as 0% for women with advanced-stage disease (stages II–IV) [9].

Improving outcomes for women with small cell carcinoma of the cervix has proven difficult because of the rarity of this disease. For patients with recurrent disease, there are no standard treatment protocols, and both the Society of Gynecologic Oncology and Gynecologic Cancer InterGroup recommend individualized treatment because of the acknowledged lack of any clinical trials to guide therapy for these women [6,7]. As outcomes are poor and therapeutic regimens are uncertain, we sought to determine whether there were common somatic mutations that might inform targeted therapy or potential clinical trials for women with recurrent small cell cancer of the cervix. Specifically, we reviewed the results in a cohort of 44 patients with small cell carcinoma of the cervix who had next generation sequencing at our institution to identify mutations in a panel of 50 genes that are commonly altered and/or targetable with existing drug inhibitors.

2. Methods

Data presented in this manuscript were abstracted from the Neuroendocrine Cervical Tumor Registry (NeCTuR) of The University of Texas MD Anderson Cancer Center. This Institutional Review Board–approved registry collects a wide range of data on women with small and large cell cervical cancers. Women who have been diagnosed with this disease or family members of deceased patients consent to participate in the registry and then provide their medical records for entry. Participants are recruited through a Facebook support group (www.facebook.com/groups/scccsisters), our website (www.necervix.com), or word of mouth. This study is a retrospective review of all patients with confirmed small cell cervical cancer (pure or mixed) who underwent molecular testing of a tumor specimen at MD Anderson Cancer Center from January 1, 2013, to December 31, 2015. Patients with pure large cell or carcinoid tumors were excluded. All pathologic specimens were reviewed by a pathologist specializing in gynecologic malignancies to confirm the histologic diagnosis of small cell neuroendocrine cervical cancer. A total of 44 patients met these inclusion criteria. Forty-three patients were seen at least once at MD Anderson for treatment and/or treatment recommendations. One patient had pathology review and molecular testing at MD Anderson but was not seen by a gynecologic oncologist at MD Anderson.

For the somatic genomic analysis, DNA was extracted, purified, and quantified from formalin-fixed, paraffin-embedded archived tissue obtained from surgery or biopsy. Next generation sequencing was performed using the Ion Ampliseq Cancer Panel (Life Technologies, Grand Island, NY) [10]. Specimens required >20% tumor cell content for analysis. The initial 8 patients (18%) had mutation hotspots assessed in 46 cancer-related genes. In July 2013, an additional 4 genes were added to the testing panel (*EZH2*, *IDH2*, *GNA11*, and *GNAQ*), and the remaining 36 patients (82%) had evaluation of all 50 genes (Table 1). This 50 gene panel was standardized for clinical molecular testing across the entire institution. These 50 genes were originally chosen as they were either commonly mutated genes in malignancies or had targeted agents either developed or in development. Additional details regarding this platform's analytic sensitivity and genomic aberration coverage are provided in the supplemental methods, available online. Details of mutational analysis are also provided in the supplemental methods.

Descriptive statistics were used to summarize patient demographic and mutation data. Patients were considered to have an actionable mutation if there currently existed an agent (approved or in development) that targeted the mutation or abnormalities in the molecular pathway of the mutation [11].

3. Results

Forty-four patients with small cell cervical cancer had molecular testing for genomic alterations. Demographics for the entire cohort are shown in Table 2. The median age was 37.5 years (range, 24.7–63.6). Thirty-eight patients (84%) had pure small cell cervical cancer and 6 (14%) had mixed small and large cell cervical cancer. Twenty-six patients (59%) had clinical stage I disease.

Tumor for molecular evaluation was obtained from the cervix in 37 patients (84%), from a lymph node in 3 patients (7%), from the vagina in 2 patients (5%), and from the lung and from a subcutaneous lesion in 1 patient each (2%). In 37 patients (84%), tumor specimens were obtained prior to initiation of therapy; in the remaining 7 patients (16%), tumor specimens were obtained from persistent disease after treatment or at time of first recurrence.

All tumor samples yielded adequate DNA for genomic sequencing. Thirty-five mutations were identified in 24 patients (55%) (Table 3). Fifteen patients (63%) had 1 mutation, 7 patients (29%) had 2 mutations, and 2 patients (8%) had 3 mutations. In all 44 patients, the most commonly seen mutations were mutations in *PIK3CA* (8 patients), *KRAS* (6 patients), and *TP53* (5 patients). Of the 24 patients who had a mutation, 21 (88%) had at least 1 alteration for which there currently existed a class of biological agents targeting that mutation. In the entire cohort of 44 patients, 48% had at least 1 actionable mutation. Details of individual mutations are shown in Supplemental material Table 1.

The median follow-up time for the entire cohort was 16.6 months (range, 0.0–45.0). At this writing, 7 patients are undergoing active primary treatment, 10 patients are without evidence of disease after primary treatment, 14 patients are alive with disease being treated for recurrence, and 13 patients are dead of disease. Of the 37 patients who have completed primary treatment, 27 (73%) have had a recurrence.

4. Discussion

In this study of 44 patients with small cell cervical cancer, a rare disease, the most commonly mutated gene was *PIK3CA*, which was mutated in more than 18% of patients. Other mutations found in more than

Table 1
Gene panel for next generation sequencing.

ABL1	*EGFR*	***GNAQ***	*KRAS*	*PTPN11*
AKT1	*ERBB2*	*GNAS*	*MET*	*RB1*
ALK	*ERBB4*	*HNF1A*	*MLH1*	*RET*
APC	***EZH2***	*HRAS*	*MPL*	*SMAD4*
BRAF	*FGFR1*	***IDH2***	*NOTCH1*	*SMARCB1*
CDH1	*FGFR2*	*JAK2*	*NRAS*	*SRC*
CDKN2A	*FGFR3*	*JAK3*	*PDGFRA*	*STK11*
CSF1R	*FLT3*	*KDR*	*PIK3CA*	*TP53*
CTNNB1	***GNA11***	*KIT*	*PTEN*	*VHL*

NOTE: Genes in boldface were added to the original panel partway through the study period (see Methods section for details).

Table 2
Patient Demographics and Clinical Characteristics.

Characteristic	Value (n = 44)
Median age (range), years	37.7 (24.7–63.6)
Median BMI (range), kg/m^2	26.2 (19.5–50.1)
Race/ethnicity, no. (%)	
Caucasian	33 (75)
Hispanic	6 (14)
Asian	3 (7)
Black	2 (4)
Histologic subtype, no. (%)	
Pure small cell	38 (86)
Mixed small and large cell	6 (14)
Stage, no. (%)	
IB1	12 (27)
IB2	14 (32)
IIA	2 (4)
IIB	2 (4)
IIIA	0 (0)
IIIB	3 (7)
IVA	0 (0)
IVB	10 (23)
Unknown	1 (2)
Specimen type, no. (%)	
Primary (untreated) disease	37 (84)
Recurrent (treated) disease	7 (16)

Abbreviation: BMI, body mass index.

10% of patients were *KRAS* (14% of patients) and *TP53* (11%). Fifty-five percent of all patients in the series had at least 1 mutation, and many of these mutations were targetable by a drug in the emerging portfolio of novel targeted agents (Table 3).

The pattern of mutations in this series of patients with small cell cervical cancer seems different from the pattern of mutations in HPV-related cervical cancer histologic subtypes, such as squamous cell and adenocarcinoma. For example, 38% of squamous cell carcinomas of the cervix and 25% of adenocarcinomas of the cervix have a *PIK3CA* mutation [12], but we found that only 18% of small cell carcinomas had this mutation. Mutations in *PIK3CA* are also commonly found in other HPV-associated malignancies, such as oropharyngeal cancer (28%) [13] and squamous cell anal cancer (22%) [14].

These differences may stem from the fact that small and large cell cervical cancers do not seem to require HPV for malignant transformation as do squamous and adenocarcinomas. The reported rates of HPV in neuroendocrine tumors of the cervix vary widely, from 53% to 100% [15–19]. Without virtually universal detection of HPV in all specimens of small cell cervical cancer, we should not assume that HPV is necessary for development of small cell cervical cancer as it is for squamous cell carcinoma and adenocarcinoma of the cervix. As the prevalence of anogenital HPV in sexually active women is greater than 80%, HPV detected in neuroendocrine cervical cancer specimens may be a reflection of carrier status as opposed to a causal factor. Furthermore, as small cell cervical cancer seems more pathologically similar to small cell lung cancer than to squamous cell or adenocarcinoma of the cervix, it is notable that small cell lung cancers have no association with HPV infection [20].

Table 3
Mutations found in patients with small cell cervical cancer.

Mutated gene[a]	*n*	% of cohort (n = 44)	Potential therapeutic targeted drugs [29]
PIK3CA	8	18	mTOR, mTORC1/2, AKT, and PI3K inhibitors
KRAS	6	14	MEK inhibitors
TP53	5	11	WEE-1 and exportin inhibitors
GNAS	3	7	None
CTNNB1	3	7	None
SMAD4	2	5	None
MET	2	5	Tyrosine kinase, MET, and HGF inhibitors
AKT1	1	2	mTOR, mTORC1/2, AKT, and PI3K inhibitors
PTEN	1	2	mTOR, mTORC1/2, AKT, and PI3K inhibitors
RB1	1	2	CDK 4/6 inhibitors
SMARCB1	1	2	None
NRAS	1	2	MEK inhibitors
FBXW7	1	2	None

NOTE: Mutations were found in 24 of the 44 patients in the cohort. Seven patients had 2 mutations, and 2 patients had 3 mutations.
[a] Exomic coverage for each of these genes is described in the supplemental methods, available online.

As more than 30,000 new cases of small cell lung cancer are diagnosed in the United States each year (compared to fewer than 150 cases of small cell cervical cancer), small cell lung cancer has been studied in depth. Inactivating mutations in *TP53* and *RB1* are seen in almost all small cell lung cancer specimens when exome sequencing is performed [21]. However, as next generation sequencing focuses on hotspot mutation identification, our experience has revealed fewer abnormalities in *TP53* and *RB1* with this method than seen in whole exome sequencing of small cell lung cancer specimens and similar underestimation of mutations may be present in small cell cervical cancer too. Researchers have also identified histone modification [21] and mutations in the SOX family of genes [22] as potentially relevant alterations in small cell lung cancer. Furthermore, *PARP1* expression is frequently seen in small cell lung cancers, and PARP inhibitors have been shown to be effective in small cell lung cancer cell lines and patients [23,24]. Whether these genetic mutations are also present in small cell cervical cancer specimens is currently under investigation by our group.

Although small cell cervical cancer is a rare tumor without a unifying mutational event at this level of interrogation, the presence of actionable events provides an opportunity to individualize therapy and to better understand the series of events that may describe this disease's unique natural history. We recently reported a patient with recurrent small cell cervical carcinoma whose tumor was found to have a *KRAS* mutation (NM_033360.2 (KRAS): c.35G>A p.G12D). She was treated with the MEK inhibitor trametinib and had a complete radiologic response after 3 cycles [25]. Of interest, the type of RAS mutation may have implications for therapeutic management. While G12D and G12V are the 2 most common *KRAS* mutations, their downstream signaling is not completely the same. The G12D variant signals primarily through the PI3K, FAK, JNK, and p38 pathways and less dependently through RAF/ERK [26,27]. In contrast, the G12V variant signals predominantly through the MAPK cascade and has lost the ability to bind to and signal through PI3K, specifically by blocking Akt activation [27]. Thus, tumor cells with G12V mutation may be more sensitive to a selective MEK inhibitor, while tumor cells with G12D mutation might require inhibitors targeting both the MAPK and PI3K pathways.

Studies in patients with uncommon tumors can be difficult; however, there currently exists a rich network of women with small cell cervical cancer on social media sites, making recruitment to protocols much more feasible [8]. We currently are characterizing tumors from a variety of small cell cancers arising at sites other than lung (cervix, uterus, bladder, prostate, colorectal, and head and neck) for a potential clinical trial of extrapulmonary small cell cancers. Although there are a variety of genetic mutations among patients with small cell cervical cancer and likely among those with small cell cancers at other sites, a trial could be designed on the basis of actionable drivers in small cell cervical cancer. A recent study in lung cancer showed that patients with mutations given therapy targeting their mutation had a hazard ratio for death of 0.69 compared to patients who had an oncogenic driver but did not receive targeted therapy [28].

Although this study included a limited number of tumor specimens, it is the first to attempt to detect genetic abnormalities in neuroendocrine carcinoma of the cervix and certainly is the largest effort to date. The testing described here, performed through our Institute for Personalized Cancer Therapy, only included analysis of mutation hotspots in 50 genes. We are currently collecting more tumor samples in order to validate our findings and expand our knowledge of potential drivers. We plan to undertake a much more expansive investigation of molecular abnormalities in small cell cervical cancer through RNA and whole exome sequencing.

In conclusion, tumors from women with small cell cervical cancer have a high likelihood of genetic mutations; however, no single mutation was found in more than 18% of specimens examined. Many small cell cervical cancers will harbor actionable driver mutations, and we are optimistic that a clinical trial designed to triage patients to biological therapy is feasible and has potential to improve outcomes in this highly aggressive disease. In the near future, we hope to have results from RNA and whole exome sequencing of small cell carcinoma to further inform therapeutic development for this highly aggressive disease.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2016.04.001.

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