GYNECOLOGY

Combination therapy with topotecan, paclitaxel, and bevacizumab improves progression-free survival in patients with recurrent high-grade neuroendocrine cervical cancer: a Neuroendocrine Cervical Tumor Registry (NeCTuR) study

Michael Frumovitz, MD; Gary B. Chisholm, MS; Anuja Jhingran, MD; Preetha Ramalingam, MD; Alejandra Flores-Legarreta, MD; Priya Bhosale, MD; Naomi R. Gonzales, MPH; R. Tyler Hillman, MD, PhD; Gloria Salvo, MD

BACKGROUND: Recurrent high-grade neuroendocrine cervical cancer has a very poor prognosis and limited active treatment options.

OBJECTIVE: This study aimed to evaluate the efficacy of the 3-drug regimen of topotecan, paclitaxel, and bevacizumab in women with recurrent high-grade neuroendocrine cervical cancer.

STUDY DESIGN: This retrospective cohort study used data from the Neuroendocrine Cervical Tumor Registry (NeCTuR), which include data abstracted directly from medical records of women diagnosed with high-grade neuroendocrine carcinoma of the cervix from English- and Spanish-speaking countries. The study compared women with recurrent high-grade neuroendocrine cervical cancer who received the topotecan, paclitaxel, and bevacizumab regimen as first- or second-line therapy for recurrence and women with recurrent high-grade neuroendocrine cervical cancer who received chemotherapy but not the topotecan, paclitaxel, and bevacizumab regimen. Patients continued chemotherapy until disease progression or the development of unacceptable toxic effects. Progression-free survival from the start of therapy for recurrence to the next recurrence or death, overall survival from the first recurrence, and response rates were evaluated.

RESULTS: The study included 62 patients who received the topotecan, paclitaxel, and bevacizumab regimen as first- or second-line therapy for recurrence and 56 patients who received chemotherapy but not the topotecan, paclitaxel, and bevacizumab regimen for recurrence. The median progression-free survival rates were 8.7 months in the topotecan, paclitaxel, and bevacizumab regimen group and 3.7 months in the non—topotecan, paclitaxel, and bevacizumab regimen group, with a hazard ratio for disease progression of 0.27 (95% confidence interval, 0.17—0.48; $P<.0001$). In the topotecan, paclitaxel, and bevacizumab regimen group, 15% of patients had stable disease, 39% of patients had a partial response, and 18% of patients had a complete response. Compared with patients in the non—topotecan, paclitaxel, and bevacizumab regimen group, significantly more patients in the topotecan, paclitaxel, and bevacizumab regimen group remained on treatment at 6 months (31% vs 67%, respectively; $P=.0004$) and 1 year (9% vs 24%, respectively; $P=.02$). The median overall survival rates were 16.8 months in the topotecan, paclitaxel, and bevacizumab regimen group and 14.0 months in the non—topotecan, paclitaxel, and bevacizumab regimen group, with a hazard ratio for death of 0.87 (95% confidence interval, 0.55—1.37).

CONCLUSION: Combination therapy with topotecan, paclitaxel, and bevacizumab was an active regimen in women with recurrent high-grade neuroendocrine cervical cancer and improved progression-free survival while decreasing the hazard ratio for disease progression.

Key words: cervical cancer, chemotherapy, high-grade neuroendocrine carcinoma, paclitaxel, small-cell carcinoma, topotecan

Introduction

Small-cell and large-cell high-grade neuroendocrine carcinomas of the cervix are highly aggressive and deadly. Neuroendocrine carcinomas of the cervix are exceedingly rare, accounting for <1.5% of all cervical cancers, which translates into approximately 200 cases per year in the United States.[1,2] Women with these malignancies are more likely to die of their disease than women with squamous cell carcinomas of the cervix of similar stage; the hazard ratios (HRs) for death are 3.0 for early-stage disease and 1.7 for locally advanced disease.[3]

As many as 80% of women diagnosed with neuroendocrine cervical cancer will have a recurrence.[4] There is no curative option for recurrence, and chemotherapy options for recurrence are limited. As neuroendocrine cervical carcinoma appears histologically similar to small-cell lung cancer, many of the chemotherapy regimens used for neuroendocrine cervical carcinoma were adopted from regimens used for small-cell lung cancer, among them single-agent cytotoxic chemotherapy regimens. However, in patients with neuroendocrine cervical carcinoma, these regimens proved insufficient as overall survival (OS) after recurrence was only 7 to 8 months.[5]

Because of the futility of the small-cell lung cancer chemotherapy regimens in most women with neuroendocrine cervical cancer, in 2013, we started treating this disease with the 3-drug regimen of topotecan, paclitaxel, and bevacizumab (TPB). Our rationale for adopting this approach was multifold. First, topotecan and paclitaxel as single agents are

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AJOG at a Glance

Why was this study conducted?

Recurrent high-grade neuroendocrine cervical cancer has limited active treatment options.

Key findings

Combination therapy with topotecan, paclitaxel, and bevacizumab (TPB) improved progression-free survival in women with recurrent disease. Moreover, women with recurrent disease who received the TPB regimen were more likely to stay on treatment for 6 and 12 months.

What does this add to what is known?

Our data markedly expanded on a previously published smaller study showing combination therapy with TPB as an active regimen in patients with recurrent high-grade neuroendocrine cervical cancer.

commonly used for recurrent small-cell lung cancer. Second, small-cell cervical cancer has high expression of the vascular endothelial growth factor receptor, so adding bevacizumab made clinical sense.[6] Finally, this 3-drug combination was safely used in the Gynecologic Oncology Group (GOG) 240 study.[7] The study included women with squamous cell carcinoma and adenocarcinoma of the cervix, many of whom had previously undergone radiation therapy. Although patients with neuroendocrine carcinoma of the cervix were excluded from that study, patients with squamous cell carcinoma and adenocarcinoma of the cervix and patients with neuroendocrine carcinoma of the cervix received similar treatment at initial diagnosis (ie, radical surgery and/or chemoradiation), so we believed that the regimen used in the GOG 240 trial would be equally well tolerated in patients with neuroendocrine cervical carcinoma.

In an earlier study, published in 2017, we compared women with recurrent neuroendocrine carcinoma of the cervix who received the TPB regimen at first recurrence (n=13) with those who received chemotherapy other than the TPB regimen at first recurrence (n=21).[8] In that small study, patients who received the TPB regimen had a significantly improved median progression-free survival (PFS) compared with patients who did not receive the TPB regimen (7.8 vs 4.0 months, respectively), with an HR for disease progression of 0.21 (95% confidence interval [CI], 0.09−0.54). The HR for death was 0.53; however, this did not meet statistical significance (95% CI, 0.23−1.22).[8] As there are few alternatives for patients with recurrent neuroendocrine cervical cancer, the TPB regimen, also called "The Texas Cocktail" by patients with this disease, has been adopted by practitioners worldwide and incorporated in multiple treatment recommendations.[9−12] This study aimed to update the experience of patients with the combination therapy with TPB and compare the outcomes in women with recurrent high-grade neuroendocrine cervical cancer between those who received the TPB regimen and those who received the non-TPB regimen.

Materials and Methods

Patients who had undergone chemotherapy for recurrent high-grade neuroendocrine cervical cancer were identified from the Neuroendocrine Cervical Tumor Registry (NeCTuR) of The University of Texas MD Anderson Cancer Center. This institutional review board (IRB)-approved registry contains data abstracted directly from medical records of women diagnosed with high-grade neuroendocrine cervical cancer from English- and Spanish-speaking countries. Women or family members of deceased women with this disease consented to participate in the registry and assisted with the retrieval of records. Patients did not need to be seen at The University of Texas MD Anderson Cancer Center to be included in the registry. To date, the NeCTuR trial includes records of 533 women with high-grade neuroendocrine cervical carcinoma. Data in NeCTuR are collected and stored using Research Electronic Data Capture tools hosted at The University of Texas MD Anderson Cancer Center.[13]

This current study evaluating the efficacy of TPB had a separate approval from The University of Texas MD Anderson Cancer Center IRB. Women included in this study had pathologically confirmed recurrent high-grade neuroendocrine cervical cancer (pure or mixed; small cell, large cell, or unclassified neuroendocrine histologic type) and had received chemotherapy as part of their therapy for recurrence. Women were divided into 2 groups: those who received the TPB regimen (TPB group) and those who did not receive the TPB regimen (non-TPB group). Women were included in the TPB group if they received the TPB regimen as first- or second-line therapy for recurrence. Women who received less than 2 cycles of chemotherapy for recurrence were excluded, as were women who received definitive chemoradiation or surgery for oligometastatic disease at first recurrence. Women included in the non-TPB group received a variety of regimens at the discretion of their treating physicians (Table 1). This updated study includes 34 patients (13 in the TPB group and 21 in the non-TPB group) who were previously reported by our team.[8]

The TPB regimen was prescribed as follows: topotecan 0.75 mg/m^2 on days 1 to 3, paclitaxel 175 mg/m^2 on day 1, and bevacizumab 15 mg/kg on day 1 on a 21-day cycle. Patients in the non-TPB group were given a variety of regimens at their physician's discretion. Therapy was continued until disease progression or the development of unacceptable toxic effects. For patients who achieved a complete response (CR) to the TPB regimen, chemotherapy was modified at the physician's discretion (eg, changed to maintenance bevacizumab or reduced

to a chemotherapy doublet). The assessment for a response was performed every 2 to 3 cycles with either computed tomography or positron emission tomography at the physician's discretion.

Descriptive statistics were used to summarize demographic and clinical characteristics, stratified by whether patients received the TPB regimen as first- or second-line therapy for recurrence. The Fisher exact test was used to compare categorical variables, excluding the "missing" category, which is presented in Table 1 but was not included in statistical testing. The Wilcoxon rank-sum test was used to compare median age and body mass index (BMI). OS was estimated from the date of the first recurrence to death or last follow-up, with patients alive at the last follow-up censored on that date. PFS was estimated from the date of treatment start after the first or second recurrence to the next recurrence or death, with patients alive without further recurrence at the last clinic visit censored on that date. OS and PFS were estimated using the Kaplan-Meier product limit estimator. Cox proportional hazards regression was used to model the OS and PFS as a function of histologic type and therapy for recurrence. Statistical analyses were performed using SAS/STAT software for Windows (version 9.4; SAS Institute, Cary, NC). Graphics were generated using R software (version 4.0.3; R Foundation for Statistical Computing).

Results

Of 118 patients, 62 received the TPB regimen as first-line (n=47) or second-line (n=15) therapy for recurrence, and 56 patients received chemotherapy but not the TPB regimen for their recurrence. There was no difference between the TPB and non-TPB groups in age, BMI, race or ethnicity, smoking history, histology, or stage at diagnosis (Table 1). Initial therapy at the time of diagnosis of neuroendocrine cervical carcinoma differed between the 2 groups (*P*=.02). In the TPB group, 79% of patients received radiation as part of their upfront treatment, whereas 73% of women in the non-TPB group underwent radiotherapy.

TABLE 1
Demographic and clinical characteristics of patients with high-grade neuroendocrine carcinoma of the cervix treated with chemotherapy as the primary therapy for the first or second recurrence

Characteristics	TPB group (n=62)	Non-TPB group (n=56)	*P* value
Age (y), mean	39.6	39.6	.99
Body mass index (kg/m^2), mean	28.1	27.1	.53
Race, n (%)			.14
Asian	4 (6)	7 (13)	
Black or African American	2 (3)	4 (7)	
White	50 (81)	30 (54)	
Other	3 (5)	5 (9)	
Missing	3 (5)	10 (18)	
Ethnicity, n (%)			.59
Not Hispanic or Latino	49 (79)	30 (54)	
Hispanic or Latino	9 (15)	8 (14)	
Missing	4 (6)	18 (32)	
Smoking history, n (%)			.46
Never	41 (66)	29 (52)	
Past	17 (27)	17 (30)	
Current	4 (6)	6 (11)	
Missing	0 (0)	4 (7)	
Histologic type, n (%)			.97
Small cell	40 (65)	34 (61)	
Large cell	6 (10)	6 (11)	
Small cell and large cell	4 (6)	5 (9)	
Undifferentiated	12 (19)	11 (20)	
Pure neuroendocrine, n (%)			.06
Yes	46 (74)	32 (57)	
No	16 (26)	24 (43)	
FIGO stage at diagnosis, n (%)			.54
IA2	1 (2)	0 (0)	
IB1	6 (10)	5 (9)	
IB2	8 (13)	5 (9)	
IB3	6 (10)	8 (14)	
IB, subcategory not reported	0 (0)	1 (2)	
IIA1	1 (2)	0 (0)	
IIA2	1 (2)	0 (0)	
IIB	2 (3)	2 (3)	
IIIB	0 (0)	1 (2)	
IIIC1	11 (18)	14 (25)	
IIIC2	4 (6)	2 (4)	

Frumovitz. Topotecan, paclitaxel, and bevacizumab for recurrent high-grade neuroendocrine cervical cancer. Am J Obstet Gynecol 2022. *(continued)*

TABLE 1
Demographic and clinical characteristics of patients with high-grade neuroendocrine carcinoma of the cervix treated with chemotherapy as the primary therapy for the first or second recurrence *(continued)*

Characteristics	TPB group (n=62)	Non-TPB group (n=56)	*P* value
IVB	22 (35)	15 (27)	
Missing	0 (0)	3 (5)	
Treatment at initial diagnosis of neuroendocrine carcinoma, n (%)[a]			.04
Radiation only	2 (3)	9 (16)	
Chemotherapy only	9 (15)	6 (11)	
Chemotherapy + radiation	26 (42)	11 (20)	
Surgery only	0 (0)	4 (7)	
Surgery + radiation	6 (10)	8 (14)	
Surgery + chemotherapy	4 (6)	5 (9)	
Surgery + chemotherapy + radiation	15 (24)	13 (23)	

TPB, topotecan, paclitaxel, and bevacizumab.

[a] Order in which modalities were received was not the same in all patients.

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There was no difference between the TPB and non-TPB groups in the time to recurrence after completion of initial therapy for their newly diagnosed neuroendocrine carcinoma (TPB group, 8.9 months; non-TPB group, 8.1 months; *P*=.57). The patients in the non-TPB group received a variety of chemotherapy regimens at the time of first recurrence (Table 2). Of note, 19 patients received a regimen containing immunotherapy at some point during their therapy for recurrence (10 in the TPB group and 9 in the non-TPB group). Of the 9 patients in the non-TPB group who received immunotherapy during their therapy for recurrence, 5 received an immunotherapy agent at the first recurrence (Table 2), whereas the other 4 received immunotherapy as the second-line therapy or beyond. Moreover, 16 of 62 patients (26%) in the TPB group and 16 of 56 patients (29%) in the non-TPB group received palliative radiation therapy in addition to chemotherapy at the first recurrence (*P*=.84).

In addition, 16 patients (26%) receiving the TPB regimen had disease progression at the first assessment. Of the remaining 46 patients, 24 (39%) had a partial response (PR), 11 (18%) had a CR, 9 (15%) had a stable disease (SD) to TPB, and 2 (3%) had an unknown response at first assessment and eventually progressed. The clinical benefit rate (CR + PR + SD) of TPB in women with high-grade neuroendocrine cervical cancer was 74%.

At the time of data lock, 22 of 118 patients with recurrence had missing data related to the dates of treatment and thus were excluded from the analysis of PFS, but all 118 patients were included in the analysis of OS. Among the 96 patients with complete dates of treatment, 59 of 61 patients (97%) who received the TPB regimen for recurrence and 45 of 45 patients (100%) who received the non-TPB regimen for recurrence had a PFS event. For these patients, the median PFS was 8.7 months (95% CI, 6.7−9.5 months) in the TPB group, compared with 3.7 months (95% CI, 2.6−6.0 months) in the non-TPB group (Figure 1). The HR for disease progression was 0.27 (95% CI, 0.17−0.48; *P*<.0001). There was no difference in PFS between pure and mixed histologic types when tested alone (*P*=.16), but histologic type was significant after the adjustment for TPB regimen and initial therapy for neuroendocrine carcinoma (*P*=.03). There was no difference in PFS among individual tumor histologic types (small cell, large cell, mixed small and large cells, and undifferentiated), either alone (*P*=.08) or after the adjustment for TPB regimen and initial treatment (*P*=.08).

Multiple sensitivity analyses were performed. When comparing those patients in the TPB group with those in the non-TPB group who got a regimen containing bevacizumab (n=12) (Table 2), the HR for disease progression remained significant at 0.26 (*P*=.001), favoring the TPB regimen. When including patients who received ≤2 cycles of chemotherapy in the analysis, the HR for disease progression remained significant at 0.5 (*P*<.0001), favoring the TPB regimen. Moreover, we evaluated whether patients who received treatment more recently had a better PFS than those who received therapy for recurrence decades ago; we adjusted the analysis for the year of treatment and continued to find that the TPB regimen continued to improve the HR for recurrence compared with non-TPB regimens (HR, 0.52; *P*=.002). Furthermore, when comparing patients who received the TPB regimen with those who did not but limiting the analysis to only those patients who recurred after 2013 when we started using the TPB regimen, the patients who received the TPB regimen continued to see a reduction in the time to disease progression (HR, 0.5; *P*=.007). Of note, 41 patients (67%) in the TPB group received the TPB regimen for >6 months, compared with 14 patients (31%) in the non-TPB group (*P*=.0004). In addition, 16 patients (26%) in the TPB group received the TPB regimen for >1 year, compared with 4 patients (9%) in the non-TPB group (*P*=.02). Moreover, 4 patients (7%) in the TPB group remained on therapy or modified therapy (eg, bevacizumab maintenance) for >2 years (*P*=.13).

The median OS from the first recurrence was 16.8 months (95% CI, 12.7−24.2 months) in the TPB group,

compared with 14.0 months (95% CI, 9.8−22.1 months) in the non-TPB group (P=.49) (Figure 2). The HR for death was 0.87 (95% CI, 0.55−1.37). There was no difference in the OS between pure and mixed histologic types, either alone (P=.18) or after the adjustment for the TPB regimen and initial treatment of neuroendocrine carcinoma (P=.37). Furthermore, there was no difference in the OS among individual tumor histologic types (eg, small cell only, large cell only, mixed small and large cell, and undifferentiated) alone (P=.11), but there is a difference after the adjustment for the TPB regimen and initial treatment (P=.0495) where the small cell is significantly better than undifferentiated (HR, 0.53; 95% CI, 0.31−0.93)

TABLE 2
Chemotherapy regimens at first recurrence of high-grade neuroendocrine carcinoma of the cervix for patients who did not receive topotecan, paclitaxel, and bevacizumab as the primary therapy for the first recurrence (n = 56)

Regimen	n
Platinum + etoposide	13
Platinum + paclitaxel	6
Platinum + paclitaxel + bevacizumab	5
Topotecan	5
Platinum + irinotecan	3
Platinum + etoposide + atezolizumab	3
Irinotecan	2
Paclitaxel	2
Paclitaxel + bevacizumab	2
Topotecan + bevacizumab	2
Docetaxel	1
Docetaxe	1
Platinum + topotecan	1
Paclitaxel + topotecan	1
Paclitaxel + atezolizumab	1
Platinum + other	1
Platinum + topotecan + bevacizumab	1
Topotecan + docetaxel + bevacizumab	1
Platinum + irinotecan + other	1
Platinum + paclitaxel + bevacizumab + pembrolizumab	1
Other	3

Regimens containing carboplatin and/or cisplatin were classified as platinum.

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Comment

Principal findings

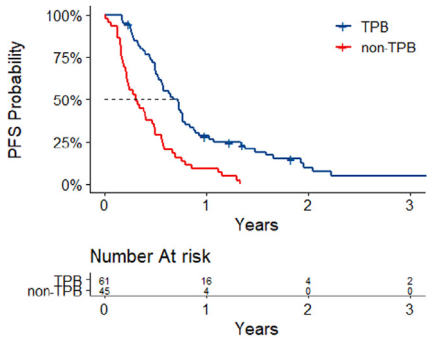
The findings from this study supported the findings from our earlier study suggesting that the TPB combination is an active regimen and improves PFS for patients with recurrent high-grade neuroendocrine carcinoma.[8] Among women treated with chemotherapy for recurrent high-grade neuroendocrine carcinoma, women who received the TPB regimen had better PFS and a decreased HR for disease progression (HR, 0.32) than women who did not receive the TPB regimen. In addition, more patients treated with the TPB regimen remained on treatment for 6, 12, and 24 months than patients treated with non-TPB regimens. Furthermore, the OS was increased for women who received the TPB regimen, although this improvement was not statistically significant.

Results in the context of what is known

This study updated our earlier study with a smaller cohort of patients published in 2017, and although the earlier study included only women with small-cell subtype who received the TPB regimen for the first recurrence, the current study included women with all high-grade neuroendocrine cervical cancer subtypes and women who received the TPB regimen as the second-line therapy for recurrence.[8] In the earlier study, which spanned 18 years, from 1998 to 2016, a total of 13 patients had received the TPB regimen. In the ensuing 5 years, an additional 49 patients in the NeCTuR database received the TPB regimen. Because very few therapeutic options exist for women with recurrent high-grade neuroendocrine carcinoma, many oncologists quickly adopted the TPB regimen after the publication of our earlier study, and multiple guidelines now include the regimen as a reasonable choice for treating recurrent disease.[9,10,12]

Interestingly, a comparison of the findings from our earlier study and the current study shows a dramatic improvement in the OS of patients in both the TPB and non-TPB groups. In 2017, the median OS rates after recurrence were 9.7 months for the TPB group and 9.4 months for the non-TPB group.[8] In this current study, the median OS rates after recurrence were 16.9 months for the TPB group and 14.0 months for the non-TPB group. The reason for this increase in OS is unknown, but the increase is not due to new treatment options as no new active therapies for neuroendocrine cervical

FIGURE 1
PFS in patients with neuroendocrine cervical cancer treated with TPB or non-TPB



PFS, progression-free survival; *TPB*, topotecan, paclitaxel, and bevacizumab.

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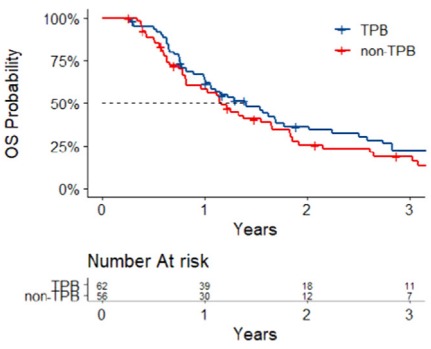
cancer have emerged over the last 5 years.

Clinical implications

After the combination therapy with TPB, patients may receive any number of chemotherapy regimens, many based on National Comprehensive Cancer Network guidelines for small-cell lung cancer. These include standard single-agent cytotoxic chemotherapy regimens, such as irinotecan, docetaxel, temozolomide, and gemcitabine, and combination chemotherapy with cyclophosphamide, doxorubicin, and vincristine. All of these regimens have minimal activity with short durations of response.[11] Recently, lurbinectedin has been approved for the treatment of recurrent small-cell lung cancer. In a phase II study of 105 patients with recurrent small-cell lung cancer, 37 patients (35%) had a PR to the drug, with a median duration of response of 5.3 months. An additional 33% of patients had an SD at the first assessment, for a disease control rate of 68%. There was no complete responder.[14] The activity of lurbinectedin in high-grade neuroendocrine cervical carcinoma remains unknown.

Another approach to treating recurrent high-grade neuroendocrine cervical cancer has been to explore targeted therapies based on molecular testing. Unfortunately, no single mutation is seen commonly in most tumors. Although tumors may harbor actionable somatic genomic alterations in *KRAS, PIK3CA, PTEN, TP53,* and *AKT1*, none of these mutations is found in more than 15% to 20% of specimens.[15–17] However, there are case reports of good responses to targeted therapies based on molecular testing. For example, Lyons et al[18] reported on a patient with recurrent small-cell cervical cancer with a *KRAS* mutation who had a CR to a MEK inhibitor. The patient ultimately experienced recurrence 9 months after initiating targeted therapy and eventually died of the disease.

FIGURE 2
OS in patients with neuroendocrine cervical cancer treated with TPB or non-TPB



OS, overall survival; *TPB*, topotecan, paclitaxel, and bevacizumab.

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Research implications

As standard chemotherapy regimens are ineffective and targeted therapies are lacking, many investigators have explored immunotherapy for women with recurrent high-grade neuroendocrine cervical cancer. Atezolizumab is commonly added to platinum and etoposide in the initial treatment of small-cell lung cancer, although its inclusion adds very minimally to survival. The IMpower-133 study (https://www.nejm.org/doi/full/10.1056/nejmoa1809064) that evaluated the combination of platinum, etoposide, and atezolizumab showed a PFS improvement of <1 month (4.3 vs 5.2 months; *P*=.02) and an OS improvement of just 2 months (10.3 vs 12.3 months; *P*=.007) for the 3-drug combination compared with platinum and etoposide alone.[19] Although these increases in survival were statistically significant, one might argue that their clinical significance is nominal especially given the additional cost of expensive immunotherapies and added toxicities. However, these modest improvements were enough to get US Food and Drug Administration approval for the combination for small-cell lung cancer, and many have used the regimen for women with neuroendocrine cervical cancer, with unknown effects.

On the basis of traditional measures that predict responsiveness to immunotherapy, one might not expect much activity of immunotherapies in women with high-grade neuroendocrine cervical cancer. For example, whole-exome sequencing has shown a low tumor mutation burden in this disease.[20] In addition, when immunohistochemistry stains were used to test for mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) in 28 different specimens from formalin-fixed, paraffin-embedded tissue blocks, all specimens were noted to have intact expression, suggesting that all specimens were microsatellite stable.[21] In that same study, only 8% of pure neuroendocrine tumors were positive for PD-L1 expression (CPS >1).[21]

However, even with multiple biomarkers predicting a low likelihood of response to single-agent PD-1 and PD-L1 inhibitors, an early case report described a CR to nivolumab in a patient with recurrent small-cell carcinoma.[22] Unfortunately, the success in that case report has not been substantiated. In a phase II basket study of pembrolizumab in 11 patients with extrapulmonary small-cell cancers, no patient met the primary endpoint of nonprogression of disease at 27 weeks.[23] This included 7 patients with gynecologic neuroendocrine cancers (6 cervical and 1 vulvar). In these women, the median PFS was 2.1 months, essentially the first radiologic assessment.[24]

Another case report detailed a CR to dual blockade using anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) in a woman with recurrent neuroendocrine cervical cancer.[25] This combination may

hold more promise than single-agent PD-1 and PD-L1 inhibitors in neuroendocrine carcinomas. The Southwest Oncology Group (SWOG)-1609 (Dual Anti-CTLA-4 and Anti-PD-1 blockade in Rare Tumors [DART]) trial was a basket trial of 32 patients with extrapancreatic neuroendocrine tumors. In the 18 patients (56%) who had high-grade neuroendocrine cancers, the overall response rate was 44%. Patients with response included 1 of 3 patients (33%) with high-grade neuroendocrine carcinoma of the cervix.[26] These promising results support our clinical trial of cadonilimab (AK104) for recurrent high-grade neuroendocrine cervical cancer (NCT05063916). This bivalent PD-1 or CTLA-4 inhibitor will be given to 18 patients with high-grade neuroendocrine cervical cancer.

Strengths and limitations

There were obvious limitations to our study, namely, its retrospective nature and small sample size. "Small sample size" is a relative term as this study included 118 patients with an exceedingly rare tumor and is the largest study comparing therapeutic approaches for recurrent high-grade neuroendocrine cervical cancer. Performing prospective therapeutic studies in patients with rare tumors remains a major challenge, and often, retrospective studies are our only means for discovering active therapeutic regimens for these patients. Fortunately, performing trials in rare tumors has become a focus for many investigators in our field, and more trials are being considered for women with rare gynecologic malignancies.[27]

Conclusion

Combination therapy with topotecan, paclitaxel, and bevacizumab is an active regimen in women with recurrent high-grade neuroendocrine cervical cancer and improves progression-free survival while decreasing the hazard ratio for disease progression. ■

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Author and article information

From the Departments of Gynecologic Oncology and Reproductive Medicine (Dr Frumovitz, Mr Chisholm, Dr Flores-Legarreta, Ms Gonzales, and Drs Hillman and Salvo), Radiation Oncology (Dr Jhingran), Pathology (Dr Ramalingam), and

Diagnostic Radiology (Dr Bhosale), The University of Texas MD Anderson Cancer Center, Houston, TX.

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Corresponding author: Michael Frumovitz, MD. mfrumovitz@mdanderson.org