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Combination therapy with topotecan, paclitaxel, and bevacizumab improves progression-free survival in recurrent small cell neuroendocrine carcinoma of the cervix

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HIGHLIGHTS

- Topotecan, paclitaxel, and bevacizumab improve PFS in small cell cervical cancer.
- The regimen showed a trend towards improved overall survival.
- Complete responses were achieved in multiple women with recurrent disease.

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ABSTRACT

Objectives. To assess if the combination of topotecan, paclitaxel, and bevacizumab (TPB) was active in recurrent SCCC and to compare the survival of patients with SCCC who received TPB to a group of women with SCCC who did not receive this regimen.

Methods. We retrospectively analyzed women with recurrent SCCC who received chemotherapy as primary therapy. Women treated with TPB for first recurrence were compared to women treated with non-TPB chemotherapy.

Results. Thirteen patients received TPB, and 21 received non-TPB chemotherapy, most commonly platinum with or without a taxane. Median progression-free survival (PFS) was 7.8 months for TPB and 4.0 months for non-TPB regimens (hazard ratio [HR] 0.21, 95% CI 0.09-0.54, $P = 0.001$). Median overall survival (OS) was 9.7 months for TPB and 9.4 months for non-TPB regimens (HR 0.53, 95% CI 0.23–1.22, $P = 0.13$). Eight women (62%) who received TPB versus four (19%) who received non-TPB regimens were on treatment for >6 months ($P = 0.02$), and four patients (31%) in the TPB group versus two (10%) in the non-TPB group were on treatment for >12 months ($P = 0.17$). In the TPB group, three patients (23%) had complete response, two (15%) had complete response outside the brain with progression in the brain, 3 (23%) had a partial response, 2 (15%) had stable disease, and 3 (23%) had progressive disease.

Conclusions. These findings indicate that TPB for recurrent SCCC significantly improved PFS over non-TPB regimens, and trends towards improved OS. Furthermore, a significant number of patients had a durable clinical benefit.

1. Introduction

Small cell cervical cancer is a highly aggressive subtype of cervical cancer hallmarked by early nodal and hematogenous spread. Even when disease is clinically limited to the pelvis, outcomes are poor; the 5-year overall survival (OS) rate for women with stage I-IIA disease is 36.8%. [1] For women with widely metastatic disease, the 5-year OS rate is 0% [2]. Similarly, recurrent disease is incurable, and survival after diagnosis of recurrent disease is short, typically only 7–8 months. [3].

Annually, small cell carcinoma of the cervix accounts for only 1–2% of the estimated 13,000 new cases of cervix cancer in the United States each year. [4] Given the rarity of the disease, clinical research has been

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limited and treatment recommendations for primary and recurrent small cell cervical cancer are based largely on the literature for small cell lung cancer, which resembles small cell cervix cancer both histologically and in its aggressive behavior. [5,6] For that reason, treatment for recurrent small cell cervix cancer has typically been single-agent therapies such as topotecan, paclitaxel, docetaxel, and irinotecan. However, in our experience, the likelihood of response to these drugs as single agents is very low, consistent with what is observed with these agents in relapsed small cell lung cancer with response rates well under 20% in most trials.

In 2013, we started prescribing a three-drug regimen of topotecan, paclitaxel, and bevacizumab (TPB) for patients with recurrent small cell cervix cancer. Our choice of this regimen was based on four factors. First, the recently published results from the GOG-0240 study showed that this regimen not only was active in women with recurrent cervix cancer but also was well tolerated by women who had previously received cisplatin-based chemoradiation as part of their primary treatment. [7] Most women with small cell cervix cancer receive chemoradiation as part of their initial therapy. [8] Second, topotecan and paclitaxel are commonly used as single agents for recurrence, but there is a biological rationale for combining them. [9] Third, previous studies have demonstrated that almost 95% of small cell cervix cancers have high expression of VEGF. [10] In GOG-0240, the addition of bevacizumab to the topotecan–paclitaxel doublet increased the objective response rate from 27% to 47% ($P = 0.002$). [7] Finally, the three-drug regimen is US Food and Drug Administration–approved for the treatment of cervix cancer, so in most instances we were able to obtain insurance approval for administration.

The primary objective of this retrospective study was to determine the clinical activity of TPB as first-line therapy for recurrent small cell cervix cancer, particularly in reference to the activity of different regimens. We also sought to evaluate the safety of TPB, with the intent to provide supporting data for a prospective clinical trial.

2. Patients and methods

We searched the Neuroendocrine Cervical Tumor Registry (NeCTuR) of The University of Texas MD Anderson Cancer Center to identify patients with small cell cervix cancer who received chemotherapy as primary therapy for first recurrence. This registry is approved by our Institutional Review Board. Women who have been diagnosed with small or large cell neuroendocrine cervix cancer or family members of deceased patients with these diseases consent to participate in the registry and provide their medical records for entry. To be eligible for the current study, patients must have had pathologically confirmed small cell cervix cancer (pure or mixed), must have received primary therapy with intent to cure, and must have received chemotherapy from January 1, 1998, to June 15, 2016 as the main therapy for first recurrence of small cell cervix cancer. Patients who received palliative radiation therapy as part of their treatment for first recurrence were included, but patients who had their first recurrence treated with either definitive radiation therapy or surgery for oligometastatic disease were excluded. Patients who had large cell or carcinoid tumors of the cervix were excluded, as were patients who received two or less cycles of chemotherapy for their first recurrence and patients who received TPB as second-line therapy for recurrence.

Patients in the TPB group received topotecan 0.75 mg/m^2 on days 1–3, paclitaxel 175 mg/m^2 on day 1, and bevacizumab 15 mg/kg on day 1 on a 21-day cycle. Patients who did not receive TPB (non-TPB group) were given a variety of regimens at the physician's discretion. All patients were continued on therapy until disease progression or development of unacceptable toxic effects. For patients who achieved a complete response to TPB, chemotherapy was modified at the physician's discretion (e.g., changed to maintenance bevacizumab or reduced to a chemotherapy doublet). Assessment for response was performed every 2–3 cycles with either computed tomography or positron emission tomography at the physician's discretion.

Study data were collected and managed using REDCap electronic data capture tools hosted at MD Anderson. [11]REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external resources.

We used descriptive statistics to summarize demographic and clinical characteristics of patients stratified by whether they received TPB (TPB group) or not (non-TPB group) for treatment of first recurrence. We used Fisher's exact test to compare categorical variables, excluding the "Not Reported" category. We used the Wilcoxon rank sum test to compare median age and body mass index between the TPB and non-TPB groups. We estimated OS from the date of treatment initiation to the date of death or last follow-up, with patients alive at last follow-up censored on that date. We estimated progression-free survival (PFS) from the date of first recurrence to the date of second recurrence or death, with patients censored on the date of last clinic visit if alive without recurrence on that date. We estimated OS and PFS using the product-limit estimator of Kaplan and Meier, and we used Cox proportional hazards regression to model OS and PFS as a function of whether patients received TPB and estimated the hazard ratio with a 95% confidence interval (CI). All statistical analyses were performed using SAS 9.3 for Windows (SAS Institute Inc., Cary, NC) and S-PLUS 8.0 for Windows (Insightful Corp., Seattle, Washington).

3. Results

Thirteen patients in the registry received TPB as primary therapy for first recurrence (TPB group), while 21 patients received a chemotherapy regimen other than TPB as primary therapy for first recurrence (non-TPB group). Regimens for the non-TPB group are listed in Table 1. Four patients (19%) in the non-TPB group received bevacizumab as part of chemotherapy for first recurrence. There was no difference between the TPB and non-TPB groups in age, body mass index, race/ethnicity, smoking history, stage at diagnosis, or initial therapy at diagnosis (Table 2). Two patients (15%) in the TPB group and six patients (28%) in the non-TBP group ($P = 0.4$) received palliative radiation therapy in addition to chemotherapy at the time of first recurrence. There was no difference between the two groups in time from completing upfront therapy to recurrence (8.6 months (TPB group) vs. 8.2 months (non-TPB group), $p = 0.82$).

Eight patients (62%) in the TPB group received TPB for >6 months, whereas only four patients (19%) in the non-TPB group received

Table 1
Chemotherapy regimens at first recurrence of small cell cervix cancer for patients who did not receive topotecan, paclitaxel, and bevacizumab as primary chemotherapy for first recurrence (n = 21).

Regimen	Number of patients
Carboplatin and paclitaxel	3
Carboplatin as a single agent	3
Paclitaxel as a single agent	3
Vincristine, cyclophosphamide, cisplatin, bleomycin, doxorubicin, and etoposide	2
Topotecan and bevacizumab	2
Paclitaxel and bevacizumab	1
Docetaxel and bevacizumab	1
Topotecan as a single agent	1
Paclitaxel and topotecan	1
Cisplatin and etoposide	1
Cyclophosphamide, doxorubicin, and vincristine	1
Carboplatin and etoposide	1
Topotecan and ME344	1

Table 2
Demographic characteristics of patients with recurrent small cell cervix cancer treated with chemotherapy as primary therapy for first recurrence.

	TPB group (n = 13)	Non-TPB group (n = 21)	*P* value
Age, mean, y	33	38	0.18
Body mass index, mean, kg/m^2	27.3	25.3	0.45
Race/ethnicity, n (%)			0.54
White	8 (62)	13 (62)	
Black	1 (8)	2 (10)	
Hispanic	3 (23)	1 (5)	
Asian	0 (0)	1 (5)	
Unknown	1 (8)	4 (19)	
Smoking history, n (%)			0.42
Never	7 (54)	12 (57)	
Past	5 (38)	5 (24)	
Current	0 (0)	3 (14)	
Unknown	1 (8)	1 (5)	
Stage at diagnosis, n (%)			0.07
IB1	2 (15)	7 (33)	
IB2	3 (23)	9 (43)	
IIB	1 (8)	1 (5)	
IIIB	3 (23)	2 (10)	
IV	4 (31)	0 (0)	
Unknown	0 (0)	2 (10)	
Primary treatment, n (%)*			0.89
Chemotherapy only	2 (15)	1 (5)	
Surgery only	0 (0)	1 (5)	
Chemoradiation only	3 (23)	6 (29)	
Chemoradiation + chemotherapy	4 (31)	4 (19)	
Surgery + chemotherapy	1 (8)	2 (9)	
Surgery + chemoradiation	0 (0)	2 (9)	
Surgery + chemoradiation + chemotherapy	3 (23)	5 (24)	

TPB, topotecan, paclitaxel, and bevacizumab.
* Note that order of modalities received may differ between patients.

chemotherapy for >6 months ($P = 0.02$). Four patients (31%) in the TPB group received TPB for >1 year, whereas only two patients (10%) in the non-TPB group received chemotherapy for >1 year ($P = 0.17$).

At first assessment, three patients (23%, 95% CI 5%–54%) in the TPB group had progressive disease, two patients (15%, 95% CI 2%–45%) had stable disease, and three patients (23%, 95% CI 5%–54%) had a partial response. All five patients with stable disease or partial response eventually progressed without ever achieving a complete response. Two patients (15%, 95% CI 2%–45%) achieved a complete response in the chest, abdomen, and pelvis but developed brain metastases while on TPB. Three other patients (23%, 95% CI 5%–54%) achieved a complete response. At this writing, one patient remains disease free at 8 months, and one remains disease free at 27 months and is currently on maintenance bevacizumab only. The final patient who achieved a complete response was unable to continue chemotherapy because of toxic effects. She received TPB for 12 cycles with continued response but was then switched to single-agent bevacizumab for 3 months because of severe fatigue and poor overall functioning. At the end of these 3 months, she was restarted on TPB. She received three cycles of TPB, during which she achieved a complete response. However, toxic effects similar to those experienced during initial treatment with TPB required changing the regimen again, this time to topotecan and bevacizumab. The patient received topotecan and bevacizumab for three cycles. At a follow-up visit 25 months after the patient started the regimen, progressive diseases including new brain metastases were noted.

At this writing, 11 of 13 patients (85%, 95% CI 55%–98%) in the TPB group and all 21 patients (100%, 95% CI 84%–100%) in the non-TPB group have had a progression-free survival (PFS) event. Median PFS for patients in the TBP group was 7.8 months (95% CI 4.5–21.8), and median PFS for patients in the non-TBP group was 4.0 months (95% CI 2.5–5.7). The effect of TPB on PFS was statistically significant (hazard ratio 0.21, 95% CI 0.09–0.54, $P = 0.001$). Kaplan-Meier PFS curves for the two groups are shown in Fig. 1.

At this writing, eight patients (62%, 95% CI 32%–86%) in the TPB group and all 21 patients (100%, 95% CI 84%–100%) in the non-TBP group have died. Median OS for patients in the TPB group was 9.7 months (95% CI 7.8–NR), and median OS for patients in the non-TPB group was 9.4 months (95% CI 6.9–10.9). Although the hazard ratio for death for patients in the TPB group was 0.53, this did not reach significance (95% CI 0.23–1.22, $P = 0.13$). Kaplan-Meier OS curves for the two groups are shown in Fig. 2.

4. Discussion

Our findings show that TPB is active in women with small cell cervix cancer and significantly prolongs PFS in these patients compared to PFS in patients who did not receive this regimen at first recurrence. Overall, 10 (77%) of 13 patients saw a clinical benefit of PFS at first assessment, and eight (62%) had a partial or complete response to therapy. Remarkably, five patients (38%) achieved a complete response of all disease outside of the brain. Finally, two patients had a durable response, remaining on therapy for >2 years after achieving a complete response, with one of the two experiencing disease progression only after therapy was discontinued because of toxicity. At this writing, a third patient remains on therapy at 8 months after obtaining a complete response.

The precise mechanism for the observed clinical activity of TPB is not clear but may be related to the relative dependency of small cell cervix cancer on angiogenesis factors in the tumor microenvironment, such as VEGF ligand expression and HIF-1α levels. [12] In addition, there may be favorable drug-drug interactions between the three compounds that make up the regimen, as was observed in GOG-0240. [7] We believe that on the basis of this promising preliminary clinical experience, TPB warrants further investigation in a prospective clinical trial.

As is reflected by the variety of chemotherapy regimens in Table 1, there is little consensus on the optimal treatment approach for patients with recurrent small cell cervix cancer. Typically, recommendations are modeled after those given to women with recurrent squamous carcinoma or adenocarcinoma of the cervix (e.g., platinum-based doublets) or recurrent small cell lung cancer (e.g., single-agent topotecan, docetaxel, or irinotecan). This lack of consensus and confounding patient characteristics make it very challenging to describe a "baseline" of anticipated clinical efficacy against which to compare the efficacy of TPB. Acknowledging these caveats, we found that considered together, these "control" regimens were associated with relatively poor outcomes (confirmed by the median PFS of 4.0 months in this study), which prompted us to pursue a new approach informed by the clinical efficacy data from GOG-0240 and biological rationale for the individual

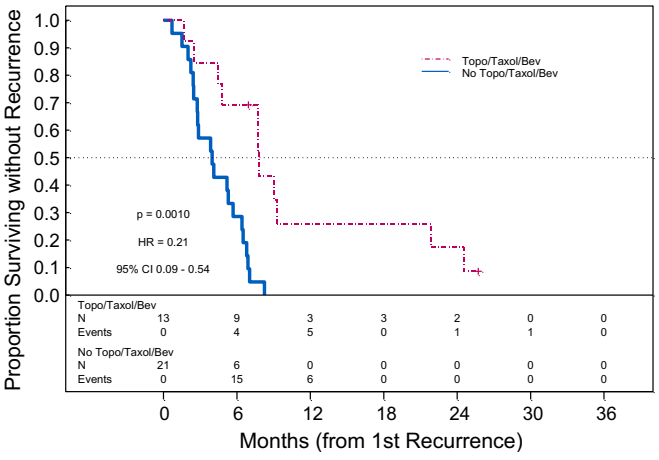

Fig. 1. Progression-free survival in patients with small cell cervix cancer treated with topotecan, paclitaxel, and bevacizumab (TPB) or only with non-TPB regimens as primary therapy for first recurrence.

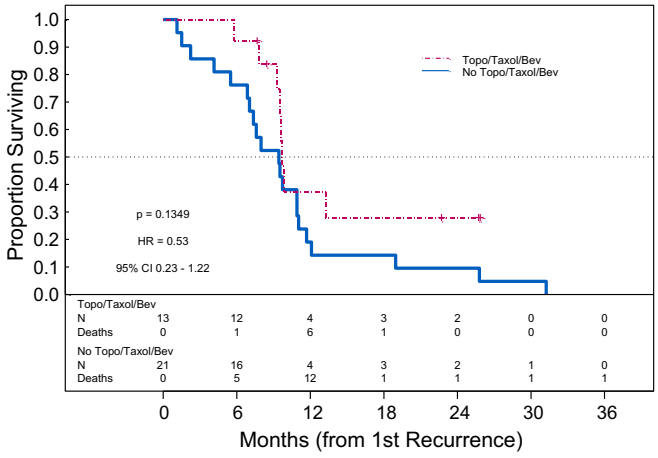

Fig. 2. Overall survival in patients with small cell cervix cancer treated with topotecan, paclitaxel, and bevacizumab (TPB) or only with non-TPB regimens as primary therapy for first recurrence.

components of the triplet. The TPB regimen has become our standard recommendation for recurrent small cell cervix cancer. [13]

Although bevacizumab as a single agent has demonstrated activity in a number of solid tumors, its independent effect in small cell carcinoma of the cervix is unknown. In recurrent small cell lung cancer, phase II studies coupling bevacizumab with various standard therapies for recurrent disease have shown mixed results. For example, paclitaxel plus bevacizumab did not significantly improve outcomes compared to single-agent paclitaxel in chemosensitive [14] or chemoresistant [15] relapsed small cell lung cancer. In contrast, a prospective study showed that the addition of bevacizumab to topotecan produced prolonged PFS compared to historical controls. [16] Similarly, a single-arm phase II study of bevacizumab plus irinotecan showed promise in improving response rates and PFS in recurrent small cell lung cancer. [17] Each of these studies in small cell lung cancer has combined bevacizumab with another drug (paclitaxel, topotecan, or irinotecan) as a doublet. To our knowledge, the triplet evaluated in our study (TPB) has not been used in relapsed small cell lung cancer.

In our study, two patients with metastatic disease in the chest, abdomen, and/or pelvis saw complete response at those disease sites but development of new tumors in the brain. The relative impenetrability of the blood-brain barrier makes delivery of drugs to the brain difficult. Topotecan does have some ability to penetrate the blood brain barrier although at concentrations only a fraction of which can be achieved in the plasma. In one study, topotecan given daily for 3 days such as given in our patient population was able to achieve concentrations in the brain 42% of that seen in the plasma. [18] Prophylactic cranial irradiation is commonly used in newly diagnosed small cell lung cancer but is not recommended in front-line treatment of small cell cervix cancer. [5, 6] We agree that prophylactic brain irradiation is not warranted in the initial treatment of small cell cervix cancer in the absence of metastatic disease; however, given our findings, prophylactic brain irradiation may be considered in patients with recurrent disease. We recently reviewed our experience in treating patients with recurrent small cell cervix cancer and found that 25% (8 of 32) developed brain metastases but only one patient had isolated brain metastases as the only site of recurrence. [24] In light of those findings, we are discussing the utility of recommending whole brain irradiation to patients with small cell cervix cancer at first recurrence in the chest, abdomen, or pelvis. At a minimum, we have begun to obtain imaging of the brain at first recurrence regardless of the presence or absence of neurologic symptoms.

One patient in our study eventually experienced disease progression after multiple breaks due to toxic effects. She was the only patient who discontinued TPB because of toxicity. This 8% discontinuation rate compares favorably with the rate in GOG-0240, in which 25% of the patients receiving bevacizumab with either topotecan and paclitaxel or cisplatin and paclitaxel discontinued because of toxicity. [7] Overall, TPB was well tolerated in our small cell cervix cancer patients, with no new toxic effects identified outside those identified in GOG-0240.

Beyond TPB, there is little to offer patients with recurrent small cell cervix cancer. We have been performing molecular testing on all patients with small cell cervix cancer in an effort to direct targeted therapeutic choices. We found that 48% of patients with small cell cervix cancer had a druggable mutation; these included mutations in *PIK3CA* (18%), *KRAS* (14%), and *TP53* (11%). [19] On the basis of molecular testing, one patient had a *KRAS* mutation identified in her tumor and was treated with a MEK inhibitor, and this patient achieved a complete response. [20]

Since small lung cancers have been predicted to have a relatively high neoantigen load, immune-based strategies may hold promise for these tumors. [21] Indeed, recent studies have demonstrated notable successes of immune checkpoint inhibitors in recurrent small cell lung cancer. In one study, single-agent pembrolizumab resulted in an overall response rate of 25% with a response duration of at least 16 weeks in all of the responders. [22] In another study, single-agent nivolumab produced an overall response rate of 10% with a disease control rate of 33%. The combination of nivolumab and ipilimumab produced a response rate of 21% and a disease control rate of 40%. [23] These are very exciting results given the historically poor response rate of <10% to traditional cytotoxic chemotherapies for patients with small cell lung cancer. As small cell cervix cancer shares histologic and clinical similarities with small cell lung cancer, we believe immune checkpoints inhibitors merit investigation for small cell cervix cancer.

The retrospective nature of this study is an obvious limitation, as is the lack of a full complement of treatment-related adverse events. Nevertheless, we believe TPB is a clinically relevant strategy in women with recurrent or persistent small cell cervix cancer and one that merits prospective evaluation. Performing prospective studies in rare tumors can be challenging. However, we believe that with active outreach through traditional means and social media, such trials are possible as patients with rare tumors typically have few other options.

Disclosure

The authors have declared no conflicts of interest.

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