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Survey article

Repeating platinum/bevacizumab in recurrent or progressive cervical cancer yields marginal survival benefits

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ABSTRACT

Our objective was to assess overall survival of cervical cancer patients following prior platinum/bevacizumab chemotherapy, comparing retreatment with platinum/bevacizumab with alternative therapies.

A retrospective analysis was performed of women who received platinum/bevacizumab (PB) chemotherapy for cervical cancer at Washington University between July 1, 2005 and December 31, 2015. Wilcoxon rank-sum exact test and Fisher's exact test were used to compare the treatment groups, and Kaplan Meier curves were generated. Cox regression analyses were performed, with treatment free interval and prior therapy response included as covariates.

Of 84 patients who received PB chemotherapy, 59 (70%) received no second line chemotherapy, as they did not recur, progressed without further chemotherapy, were lost to follow up, or expired. Of the remaining 25 patients, 9 were retreated with the combination of platinum/bevacizumab (PB), 6 were retreated with a platinum regimen without bevacizumab (P), and 10 were retreated with neither (not-P). The only long-term survivor was in the not-P group and was treated with an immunotherapy agent. Median overall survival of all patients was 7.1 months. There was a marginal difference in survival between women in the PB and not-PB groups (11.8 versus 5.7 months; HR 3.02, 95% CI, 0.98–9.28). There was no difference in survival based on platinum interval (HR 0.81; 95% CI, 0.27–2.45).

Outcomes are grim for women retreated after platinum/bevacizumab therapy and are only marginally improved by retreatment with a platinum/bevacizumab regimen. Rather than additional PB therapy, women with cervical cancer who recur after platinum/bevacizumab should consider supportive care or clinical trials.

1. Introduction

Although largely preventable through screening and vaccination (Sasieni et al., 1996; Harper & DeMars, 2017; Rijkaart et al., 2012), cervical cancer remains a deadly disease, with especially poor outcomes following diagnosis of advanced or recurrent cervical cancer (Peiretti et al., 2012; Hequet et al., 2013; Moore, 2008). Cure of recurrent metastatic cervical cancer is rare (Khoury-Collado et al., 2007). Combining platinum agents with bevacizumab can lead to dramatic and prolonged disease response among women with metastatic cervical cancer (Tewari et al., 2014; Zighelboim et al., 2013). Previously, median survival after treatment with cisplatin was only 6.5 months (Long et al., 2005), augmented by adding a second agent, such as topotecan or paclitaxel, to 9–13 months (Monk et al., 2009). Adding bevacizumab to the combination of cisplatin and paclitaxel increased the median survival to up to 17 months, and a substantial proportion of women treated with a platinum/bevacizumab combination have had complete responses and have survived for relatively long periods free of disease (Tewari et al., 2014; Zighelboim et al., 2013). However, previously unexplored is whether retreatment will have similar results.

Because the introduction of bevacizumab to combination chemotherapy regimens has been so recent, there is insufficient evidence to guide counseling for cervical cancer patients who require retreatment after prior platinum/bevacizumab therapy. Critical questions include whether to attempt treatment again with a platinum drug and whether to incorporate bevacizumab into the new regimen. It is also unclear what prognosis women might expect after retreatment. This study aims to assess overall survival after subsequent chemotherapy for women who recur after prior treatment with platinum/bevacizumab chemotherapy and to compare survival after re-treatment with platinum/

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Table 1
Patient demographics and initial treatment regimens.

					Not-PB					
	PB N = 9 (%)		Not-PB N = 16 (%)		P N = 6 (%)		Not-P N = 9 (%)		Immunotherapy N = 1	p-value *
Age at initial PB, median (range)	52.0	(36.0–63.0)	48.5	(22.0, 67.0)	58.0	(33.0–67.0)	44.0	(22.0, 54.0)	64.0	0.57
FIGO_stage2										0.44
I	1	(11.1)	5	(31.3)	1	(16.7)	3	(33.3)	1	
II	2	(22.2)	6	(37.5)	4	(66.7)	2	(22.2)	0	
III	2	(22.2)	2	(12.5)	0	(0.0)	2	(22.2)	0	
IV	4	(44.4)	3	(18.8)	1	(16.7)	2	(22.2)	0	
Histology										0.25
Squamous cell carcinoma	5	(55.6)	12	(75.0)	4	(66.7)	7	(77.8)	1	
Adenocarcinoma	2	(22.2)	4	(25.0)	2	(33.3)	2	(22.2)	0	
Adenosquamous	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	
Small cell	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	
Race										1.00
White non-Hispanic	8	(88.9)	13	(81.3)	4	(66.7)	8	(88.9)	1	
African American	1	(11.1)	2	(12.5)	1	(16.7)	1	(11.1)	0	
Asian	0	(0.0)	1	(6.3)	1	(16.7)	0	(0.0)	0	
Insurance status										0.35
Medicare/Private	8	(88.9)	10	(62.5)	3	(50.0)	6	(66.7)	1	
Medicaid/Self-Pay	1	(11.1)	6	(37.5)	3	(50.0)	3	(33.3)	0	
Smoking status										0.86
Current	2	(22.2)	5	(31.3)	2	(33.3)	3	(33.3)	0	
Former	1	(11.1)	3	(18.8)	1	(16.7)	2	(22.2)	0	
Never	6	(66.7)	8	(50.0)	3	(50.0)	4	(44.4)	1	
Initial therapy										0.35
Cisplatin + radiation	5	(55.6)	12	(75.0)	5	(83.3)	6	(66.7)	1	
Surgery + chemoradiation	2	(22.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	
Radiation	0	(0.0)	1	(6.3)	0	(0.0)	1	(11.1)	0	
Chemotherapy	1	(11.1)	1	(6.3)	1	(16.7)	0	(0.0)	0	
Other chemotherapy + radiation	1	(11.1)	2	(12.5)	0	(0.0)	2	(22.2)	0	

* For the comparison of women receiving platinum-bevacizumab combination therapy vs women receiving other regimens.

bevacizumab chemotherapy to survival after other regimens.

2. Materials and methods

This study was approved by Washington University's Institutional Review Board. We identified all patients treated concomitantly with a platinum agent and bevacizumab for cervical cancer at Washington University between July 1, 2005 and December 31, 2015 using a database of gynecologic cancer patients. A retrospective chart review was performed. We identified 84 patients who received a combination therapy of a platinum and bevacizumab (PB) for cervical cancer. These patients received platinum and bevacizumab therapy in combination with either a taxane, topotecan or alternative regimen. The use of cisplatin/taxol/bevacizumab, as described in GOG 240, was not a requirement for inclusion.

We used descriptive statistics to summarize demographic and clinical characteristics of patients, stratified by which treatment they received for their second recurrence or progressive disease (PB for platinum-bevacizumab retreatment and not-PB for treatment with an alternate regimen). The not-PB group was divided into those who received a platinum agent as part of the treatment for the recurrence or progressive disease (P) and those who did not (not-P). Progression through the initial PB treatment for a first recurrence was defined by the RECIST criteria or by the interpretation in the attending oncologist's notes. Overall survival was calculated to be the time from the day of the first chemotherapy cycle for treatment of their recurrence or progressive disease (T = 0) to the date of death. Dates of death were found either in our hospital's electronic medical record or through a search of public obituaries.

Due to the small sample size and non-normality feature of the data, Wilcoxon rank-sum exact test was conducted to compare the medians of the continuous variables, and Fisher's exact test was performed to compare the proportions of the categorical variables between the treatment groups, PB and not-PB. Kaplan Meier curves were generated, and a log-rank test was used for the comparison of survival distributions between the treatment groups as well as the treatment free interval < 6 months and ≥ 6 months.

Cox regression analyses were performed to estimate unadjusted hazard ratios and adjusted hazard ratios. In addition to the variable of interest (bevacizumab vs non-bevacizumab containing therapy) factors associated with overall survival at a significance level of P = 0.25 or lower were entered into multivariable analysis. Treatment free interval and prior therapy response were included in the regression models as covariates. When excluding the one case of immunotherapy, there was no censored case in our study cohort. Thus, Wilcoxon rank-sum exact test was conducted to compare the survival time medians between treatment groups as well as between the treatment free interval groups. All statistical analyses were performed using SAS (Version 9.4, SAS Institute Inc., Cary, NC). P-value < 0.05 was considered to be statistically significant.

3. Results

Eighty-four patients were identified who were treated with platinum-bevacizumab at our institution between July 1, 2005 and December 31, 2015. Of these, 59 received PB as their ultimate therapy, because they did not recur (n = 15), they progressed without further chemotherapy (n = 6), they were lost to follow up (n = 9), or they expired (n = 29). One of these patients was excluded because she developed myelodysplastic syndrome after the diagnosis of cervical cancer recurrence and was therefore unable to receive chemotherapy specific to cervical cancer. We identified 9 patients who received a platinum agent and bevacizumab and who were subsequently retreated with a platinum/bevacizumab combination (PB). Sixteen patients received PB followed by a subsequent, not-PB, chemotherapy (not-PB), including 6 retreated with a platinum (P) and 10 treated with a

Table 2
Characteristics and outcomes of initial and subsequent chemotherapy treatments.

					Not-PB					
	PB N = 9		Not-PB N = 16		P N = 6		Not-P N = 9		Immunotherapy N = 1	p-value*
Number of cycles - initial PB, median (range)	6.0	(3.0, 9.0)	6.0	(2.0, 12.0)	7.0	(3.0, 12.0)	6.0	(2.0, 11.0)	6.0	0.83
Response to initial PB										0.20
Complete Response	4	(44.4)	3	(18.8)	2	(33.3)	0		1	
Stable/progression	5	(55.6)	13	(81.3)	4	(66.7)	9	(100.0)	0	
Treatment free interval in months, median (range)	6.3	(0.7, 15.4)	1.6	(0.6, 19.8)	5.1	(1.2, 19.8)	1.2	(0.6, 3.2)	10.7	0.25
≤ 6mon	4	(44.4)	12	(75.0)	3	(50.0)	9	(100.0)	0	0.20
> 6mon	5	(55.6)	4	(25.0)	3	(50.0)	0		1	
Number of cycles - subsequent treatment, median (range)	6.0	(3.0, 9.0)	3.0	(1.0, 8.0)	3.5	(1.0, 8.0)	3.0	(1.0, 4.0)	3.0	0.008
Response to subsequent treatment										1.00
Partial Response	0		1	(6.3)	1	(16.7)	0		0	
Stable/progression	8	(88.9)	15	(93.8)	5	(83.3)	9	(100.0)	1	
Unknown (Lost to follow up after treatment completion)	1	(11.1)		0	0		0		0	
Reason for discontinuation of subsequent treatment										1.00
Progressive disease	7	(77.8)	13	(81.3)	5	(83.3)	8	(88.9)	0	
Toxicity	1	(11.1)	1	(6.3)	0		0		1	
Pursuit of alternative treatments	1	(11.1)	2	(12.5)	1	(16.7)	1	(11.1)	0	

* For the comparison of women receiving platinum-bevacizumab combination therapy vs women receiving other regimens.

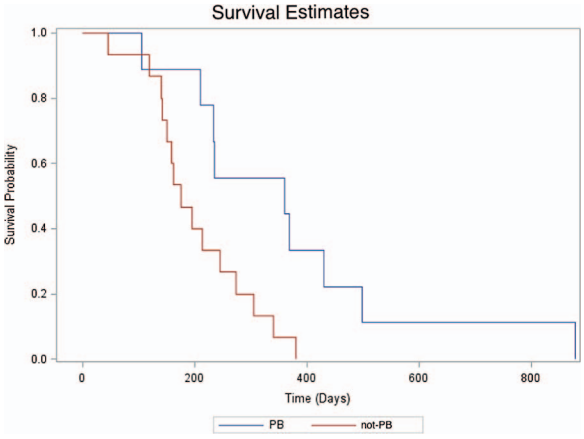
non-platinum regimen (not-P). There were no patients treated with bevacizumab maintenance therapy.

As shown in Table 1, of twenty-five patients included in the analysis, we did not identify differences in age, race, stage, histology, insurance status and smoking status between the PB and not-PB groups. Results of initial and subsequent therapy are shown in Table 2. Most women had received cisplatin and radiation as initial therapy, prior to recurrence and treatment with platinum/bevacizumab (5/9 in the PB group and 12/16 in the not-PB group). All but two patients received initial PB for recurrent cervical cancer. Of the two who received initial PB as their first treatment, one was in the PB group and one in the P group. We found no differences in the number of cycles of initial PB treatment; the median number of cycles for women in the PB and not-PB groups was each 6. We also found no differences between the two groups in their responses to the initial PB treatment.

As shown in Table 2, responses to subsequent treatment were low: 0% of PB patients and only 6% of not-PB patients had a partial response to retreatment (p = 1.00). 88.9% of PB patients and 93.8% of not-PB patients had stable or progressive disease following subsequent chemotherapy. One PB patient elected to pursue alternative treatments after completion of PB re-treatment prior to imaging documenting disease status. In all patients, the primary reason for discontinuation of subsequent treatment regardless of therapy was disease progression.

Of all patients included in the study, median survival was 7.1 months (range 1.5–28.8 months). All died except one treated with immunotherapy with attenuated Listeria encoding HPV16 E7, who was excluded from further analyses. As shown in Fig. 1, compared to women in the PB group, women in the not-PB group lived 6.1 fewer months (11.8 months in the PB group; 5.74 months in the not-PB group, HR 3.20; 95% CI, 1.19–8.60). Because of their marginal association with survival (P = 0.25), we adjusted for treatment free interval and prior therapy response; after adjustment, the difference in survival between the two groups was marginal (HR 3.02; 95% CI, 0.98–9.28). Although few patients survived > 15 months, one patient did live for almost 2.5 years after initiating retreatment with PB.

We sought evidence for "platinum sensitivity" among women re-treated with platinum after initial PB therapy. We compared those who received platinum as a component of their subsequent treatment, including the PB (n = 9) and P groups (n = 6). Survival curves of these two groups are shown in Fig. 2. Patients with more than a 6-month interval between the last cycle of their initial PB regimen and the first cycle of their subsequent treatment (either PB or P) lived only



		Unadjusted HR (%95 CI), P	*Adjusted HR (%95 CI), P*
Treatment	PB	Reference	Reference
	not-PB	**3.20 (1.19-8.60), 0.021**	3.02 (0.98-9.28), 0.053*

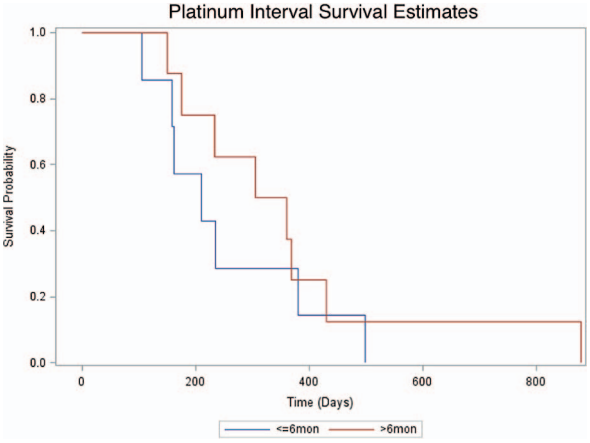
* Adjusted for interval between initial and subsequent treatment and prior therapy response.
HR, Hazard ratio; CI, Confidence interval.

Fig. 1. Overall survival estimates: Comparing re-treatment with platinum/bevacizumab and treatment with an alternative regimen.

3.4 months longer than those with treatment-free intervals of less than or equal to 6 months (HR 0.81; 95% CI, 0.27–2.45).

4. Discussion

Our study suggests that subsequent treatment with platinum/bevacizumab after previous treatment with the same yields a negligible response rate with a marginal impact on survival. *Re*-treatment of metastatic cervical cancer with PB combinations after prior PB combination therapy only occasionally resulted in long-term remission, with a median survival of 11.8 months. While just above the threshold for statistical significance and limited by the small sample size, these findings are suggestive, and should prompt others to explore this question. Any decision to re-treat with PB must be carefully discussed and considered by the oncologist and patient. One notable finding of this study was that the only patient to survive received not PB re-treatment but an experimental immunotherapy agent. As Ring et al. have demonstrated, differences between the density of cytotoxic T cells in intra- and peritumoral stroma make immunotherapy targets a



		Unadjusted HR (%95 CI), p	*Adjusted HR (%95 CI), p*
Interval between initial PB and subsequent treatment	<= 6 months	Reference	Reference
	>6 months	0.66 (0.23-1.90), 0.443	0.81 (0.27-2.45), 0.709*

* Adjusted for treatment group and prior therapy response.

Fig. 2. Exploring the platinum-free interval: Overall survival comparison between patients re-treated with a platinum chemotherapy within six months versus after six months.

potential future for treatment of recurrent cervical cancer (Ring et al., 2017). Similarly, Howitt et al. have suggested that therapies targeting PD − 1 may prove beneficial in these patients, who have few other options (Howitt et al., 2016). Given these findings, as well as ours, women with cervical cancer who have persistent or progressive disease after a first course of PB should be counseled to consider clinical trials, including immunotherapy, or supportive care, given that further conventional chemotherapy does not only not lead to cure, but is also unlikely to result in substantial additional survival time.

We did not find evidence to support a concept of "platinum sensitivity" after prior platinum therapy for cervical cancer. We analyzed patients who were re-treated with platinum therapy and compared their survival based on their treatment free intervals (TFI). While those with a TFI of > 6 months survived three months longer, this was neither statistically nor clinically significant. However, this should be validated by studies that include patients who receive therapies other than platinum/bevacizumab, as had been a specific inclusion criteria for this investigation. Others have previously investigated the concept of platinum sensitivity in cervical cancer, but with differing opinions. Takekuma et al. found that a PFI of 12 months had a strong relationship to the response to subsequent chemotherapy, but the study focused on re-administration of cisplatin versus a cisplatin analog (Takekuma et al., 2015). Matoda et al. found that a PFI of 24 months was the discriminating point in response difference (Matoda et al., 2013), however, we had no patients with greater than a 24 month TFI so were unable to replicate the analysis.

Limitations of this study include that it was a retrospective study at a single institution, therefore limited by the specific trends of chemotherapy use among a small group of physicians. It was also limited in the fact that we were naturally unable to include women who have been treated with PB for a first recurrence but have subsequently not recurred. At our institution, many of these women completed initial treatment with PB in the last 3 years, and as such, we do not yet have the data on their response to a subsequent recurrence's treatment. Since the use of the PB combination therapy is relatively new, future studies are necessary to evaluate how this chemotherapy trend affects outcomes. Larger series are needed to assess whether women who showed complete response to an initial PB treatment have increased survival when they are retreated with the same.

This study was also limited in that there was no control for downstream chemotherapies following subsequent PB treatment. Four out of the 9 patients in the PB group were treated with a chemotherapy regimen following subsequent PB. One of these patients was treated with two subsequent regimens; she progressed on each. Similarly, four patients in the not-P group received subsequent chemotherapy treatments. One received three future therapies and progressed on each.

In conclusion, women with cervical cancer after PB therapy face difficult choices, and supportive care may be a rational option for many. Retreatment with PB is associated with marginally better survival but few patients survive beyond a year. Clinical trials may offer the best hope.

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