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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