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Case series

Bevacizumab induced hypertension in gynecologic cancer: Does it resolve after completion of therapy?☆

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ABSTRACT

Hypertension (HTN) induced by bevacizumab is a side effect that is often thought to resolve after treatment. However, there are currently no reports on rates of resolution. We assess the incidence and timing of the resolution of bevacizumab induced HTN.

We evaluated all patients treated with bevacizumab for gynecologic malignancies at a single institution from 2012 through 2014. HTN was retrospectively diagnosed and staged by CTCAE v4.0 criteria. Resolution of HTN was defined as ≥2 values return to baseline blood pressure and/or discontinuation/decrease of blood pressure medications.

We identified 104 patients; 35 were excluded due to receiving bevacizumab at time of analysis. Grade 2 or higher induced HTN was identified in 34/69 (49.3%) patients, of which 26/69 (37.7%) had grade 2 HTN and 8/69 (11.6%) had grade 3/4 HTN. Onset of HTN occurred at a median of 67 (14–791) days. Resolution of HTN occurred in 28/34 (82.4%) patients with a median time to resolution of 87 (3–236) days. BMI, history of HTN, blood pressure medications, prior bevacizumab treatment, number of bevacizumab cycles, CA-125 and albumin at initiation of treatment were not independent risk factors associated with developing HTN in multivariate analysis. Median PFS for those with HTN was 12.5 (1.9–45.8) months vs 11.0 (2.1–44.7) for those without ($p = 0.17$).

Hypertension induced by bevacizumab resolved in 82% of patients in a median of 87 days. There were no identifiable risk factors associated with induced HTN and HTN was not a biomarker for improved prognosis in our cohort.

1. Introduction

Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor (VEGF) and is approved by the US FDA for colorectal cancer, renal cell cancer, glioblastoma, non-small cell lung cancer, ovarian cancer and cervical cancer. Although FDA approval for gynecologic malignancies was only obtained in 2014, Bevacizumab has been utilized as an adjuvant or single agent chemotherapy for well over a decade.

Hypertension (HTN) associated with the use of bevacizumab is one of the most common side effects reported in the literature across oncologic fields. Meta-analyses have demonstrated overall incidence of hypertension ranging from 2.7 to 32% and incidence of grade 3 or 4 HTN ranging from 1.8 to 22% (Ranpura et al., 2010). Incidence of grade 3 or 4 HTN when treating gynecologic malignancies ranges from 17–25% (Burger et al., 2011; Perren et al., 2011; Aghajanian et al., 2012; Tewari et al., 2014). If uncontrolled, hypertension can lead to many significant medical comorbidities such as heart disease, stroke, and kidney disease. When hypertension is iatrogenically induced from cancer related therapy, it is imperative for providers to understand, and report to patients, the expected duration and risks.

The half-life of bevacizumab is estimated to be approximately 20 days (range 10–50 days) with doses of 1–20 mg/kg either weekly or every three weeks (Syrigos et al., 2011). This infers that time to drug clearance would be an estimated 100 days (5 half-lives). Time analysis of onset and resolution of bevacizumab induced hypertension is limited within the current literature. It is our hypothesis that hypertension will resolve with drug clearance of 100 days. The primary objective of this study was to identify the duration and rate of resolution for bevacizumab induced hypertension. Secondary analysis were performed to evaluate incidence of hypertension, identification of risk

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factors for induced hypertension, and evaluation of prognosis in those with induced hypertension compared to those without.

2. Methods and materials

All patients treated with bevacizumab for gynecologic malignancies at a single institution from 2012 through 2014 were reviewed. Approval was obtained from the Institutional Review Board (IRB). Blood pressure values were obtained and reviewed from all clinic visits prior to, during, and post bevacizumab therapy. HTN was diagnosed based on ≥2 recorded elevated blood pressure values in the medical record and staged by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 published by the National Institutes of Health and the National Cancer Institute (Table 1). Resolution of HTN was defined as ≥2 values of a return to baseline blood pressure and/or discontinuation/decrease of blood pressure medications. Patients with preexisting HTN were graded with the same criteria and noted as preexisting controlled HTN if ≤grade 1 HTN at time of presentation. Bevacizumab induced HTN was diagnosed in patients with preexisting HTN if there was an elevation of grade by CTCAE criteria from their presenting pretreatment baseline blood pressure. All demographic and clinical information was abstracted from the medical chart. This information included age, BMI, malignancy, history of HTN and/or blood pressure medication use, bevacizumab treatment history, and presenting lab values of CA-125 and albumin. Baseline medical comorbidities were quantified using the Charlson Comorbidity Index (CCI). The CCI is a validated instrument used to estimate risk of death. It is a weighted index that assigns a score based on medical comorbidities such as coronary artery disease, diabetes, kidney or liver disease, or metastatic solid tumors. All patient deaths related to disease at time of analysis were noted and PFS was calculated as length of time from initiation of bevacizumab treatment to documented date of disease progression or recurrence by radiography and/or provider.

Study data was collected and managed using the Research Electronic Data Capture (REDCap). Descriptive statistics and tests of normality were computed. Kolmogorov-Smirnov tests were used to assess normality of continuous variables. Non-normally distributed data were compared using Mann-Whitney U tests. Continuous variables were compared with Student's *t*-tests. Dichotomous were compared using chi-square or Fisher's exact test for comparisons with cells <5. Kaplan-Meier was used to compute median time to resolution of HTN and a survival curve. Statistical analysis was performed using IBM SPSS version 23.

Table 1
CTCAE v4.0 (U.S. Department of Health and Human Services, NIH, 2009.)

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Prehypertension (systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg)
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).	Stage 1 hypertension (systolic BP 140–159 mm Hg or diastolic BP 90–99 mm Hg); medical intervention indicated; recurrent or persistent (≥24 h); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent (≥24 h) BP > ULN; monotherapy indicated
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.	Stage 2 hypertension (systolic BP≥160 mm Hg or diastolic BP≥100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated
Grade 4	Life-threatening consequences; urgent intervention indicated.	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
Grade 5	Death related to adverse event.	Death

3. Results

Of the 104 patients identified, 35 were excluded as they were still receiving bevacizumab at the time of analysis. Patient characteristics are presented in Table 2. Median follow-up time was 17.5 (2–50) months. Overall incidence of ≥grade 2 bevacizumab induced hypertension was 49.3% (34/69). The majority of HTN requiring treatment was grade 2 with 26/69 (37.7%) and 8/69 (11.6%) patients had grade 3 or 4 (Table 3).

Median number of bevacizumab cycles in those with HTN was 11 (3–57) compared to 8 (1–49) in those without HTN ($p = 0.09$). Ninety four percent (65/69) of patients received dosing of 15 mg/kg every three weeks, six patients received 10 mg/kg every two weeks. Of these six patients, 2 received dosing of 15 mg/kg every three weeks during primary treatment and were reduced to 10 mg/kg every two weeks for maintenance therapy, three patients received single agent treatment of 10 mg/kg every two weeks for recurrent disease, and one patient received 10 mg/kg every two weeks on trial.

Onset of HTN occurred at a median of 67 (14–791) days. Resolution of HTN after the last dose of bevacizumab occurred in 28/34 (82.4%) patients with a median of 87 (3–236) days. Analysis of all patients who developed HTN, including those who did not resolve in the study period, demonstrates a median time to resolution of 104 days (Fig. 1). Of the 34 patients with bevacizumab induced HTN, 16/34 (46%) had an elevation of BP to ≥grade 2 HTN who had a pre-existing diagnosis of ≥grade 2 HTN that was controlled on medications prior to initiation of bevacizumab, compared to 14/35 (40%) patients who had an elevation of BP to ≥grade 2 HTN who previously had no HTN or grade 1 HTN. In patients requiring initiation of at least one new blood pressure medication, there was no consistency in type of medication started. Nine patients received diuretics, four β-blockers, seven angiotensin-converting-enzyme inhibitors (ACE-I), two angiotensin II receptor blockers (ARB), three calcium channel blockers (CCB), and one α-blockers. Ten patients were either on a β-blocker prior to initiation of bevacizumab or started on one during treatment. Median progression free survival (PFS) for those with HTN was 12.5 (1.9–45.8) months compared to 11.0 (2.1–44.7) for those without HTN ($p = 0.17$). Median PFS in patients with HTN on a β-blocker was 11.5 (4.0–21.9) months.

Table 2
Characteristics of those with and without bevacizumab induced HTN.

	HTN n = 34	No HTN n = 35	p-value
Age (years; mean ± SD)	58.6 ± 11.6	57.3 ± 7.4	0.56
BMI (kg/m^2; median (range))	25.3 (19.7–46.4)	24.6 (17.5–125.0)	0.59
Malignancy			0.11
Ovary	32 (94.1%)	28 (80.0%)	
Uterine	0	4 (11.4%)	
Cervix	2 (5.9%)	3 (8.6%)	
Hx of HTN	16 (47.1%)	14 (40.0%)	0.55
Prior BP medication use	13 (81.3%)	10 (71.4%)	0.53
Prior bevacizumab exposure	4 (11.8%)	5 (14.3%)	1.0
Number of bevacizumab cycles (median (range))	11 (3–57)	8 (1–49)	0.09
CA-125[a] (median (range))	358 (24–8107)	300 (12–6980)	0.48
Albumin[b] (g/dL; median (range))	3.8 (2.9–4.5)	3.7 (2.8–4.5)	0.35
Charlson Comorbidity Index score (median (range))	7.5 (0 − 12)	7 (2 − 10)	0.61
PFS (months; median (range))	12.5 (1.9–45.8)	11.0 (2.1–44.7)	0.17

[a] CA-125 at initiation of bevacizumab treatment.
[b] Albumin at initiation of bevacizumab treatment.