Clinical Course of Advanced Non–Small-Cell Lung Cancer Patients Experiencing Hypertension During Treatment With Bevacizumab in Combination With Carboplatin and Paclitaxel on ECOG 4599

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ABSTRACT

Purpose

Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor (VEGF) with demonstrated efficacy in combination with carboplatin and paclitaxel (PCB) for the treatment of advanced non–small-cell lung cancer (NSCLC). Administration of bevacizumab is postulated to decrease nitric oxide synthesis and lead to hypertension, which may be a physiological sign that the VEGF pathway is more actively being blocked and could result in improved outcomes.

Patients and Methods

Eastern Cooperative Oncology Group (ECOG) 4599 randomly assigned patients with nonsquamous NSCLC to carboplatin and paclitaxel (PC) versus PCB. Hypertensive patients were compared with nonhypertensive patients with respect to overall survival (OS) and progression-free survival (PFS) using blood pressure data and adverse event data separately. High blood pressure (HBP) by the end of cycle 1 was defined as blood pressure $> 150/100$ at any previous time or at least a 20-mmHg increase in diastolic blood pressure from baseline.

Results

In a multivariable Cox model adjusting for HBP as a time-varying covariate, comparing those on PCB with HBP with those on PC gave an OS hazard ratio (HR) of 0.60 (95% CI, 0.43 to 0.81; $P = .001$); comparing those on PCB without HBP with those on PC alone, the OS HR was 0.86 (95% CI, 0.74 to 1.00; $P = .05$). Comparing the PCB HBP group with PC gave an adjusted PFS HR of 0.54 (95% CI, 0.41 to 0.73; $P < .0001$) and comparing those on PCB without HBP to those on PC, the HR was 0.72 (95% CI, 0.62 to 0.84; $P < .0001$). The 6-month cumulative incidence of hypertension was 6.2% (95% CI, 3.9% to 8.6%).

Conclusion

Data from ECOG 4599 suggest that onset of HBP during treatment with PCB may be associated with improved outcomes, and additional studies of the downstream effects of VEGF suppression and hypertension are needed.

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INTRODUCTION

The antineoplastic agent, bevacizumab, is a recombinant humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF) and prevents it from binding to its receptor, thereby delaying tumor growth and metastasis.^{1,2} It is the first antiangiogenic agent to receive approval from the US Food and Drug Administration for the treatment of several types of cancer. In combination with intravenous fluorouracil-based chemotherapy, bevacizumab improved outcomes for patients with metastatic colorectal cancer as first- or second-line therapy,³⁻⁵ and in combination with paclitaxel, the

drug showed an improvement in progression-free survival (PFS) for women with HER2-negative metastatic breast cancer.⁶ Bevacizumab has also demonstrated efficacy in combination with carboplatin and paclitaxel for the treatment of advanced-stage, nonsquamous non–small-cell lung cancer (NSCLC).⁷

Treatment with bevacizumab is associated with increased risk of toxicity: gastrointestinal perforations, nongastrointestinal fistulas, wound healing complications, hemorrhage, arterial thrombotic events, reversible posterior leukoencephalopathy syndrome, neutropenia and infection, proteinuria, and congestive heart failure have

all been documented.⁸ Bevacizumab is also associated with a higher rate of hypertension. With an overall prevalence of 11% to 16% of patients requiring intervention with antihypertensives while on therapy,^{9,10} hypertension is one of the most documented yet reversible adverse effects of bevacizumab.

Detailed studies of the VEGF pathway have revealed the mechanism by which bevacizumab affects blood pressure (BP). Antagonism of VEGF decreases nitric oxide production and leads to constriction of the vasculature and a reduction in sodium ion renal excretion, which ultimately leads to increased BP.^{11,12} Hypertension may also be a consequence of vascular rarefaction, a depletion of the arterioles and capillaries, caused by the inhibition of angiogenic growth factors required to construct new capillaries and recruit endothelial progenitor cells.¹³⁻¹⁸

Hypothesizing that the onset of hypertension during treatment denotes successful blockage of the VEGF pathway, studies have examined the relationship between hypertension and outcome among patients treated with bevacizumab. In the correlative study accompanying the Eastern Cooperative Oncology Group (ECOG) 2100 study of metastatic HER2-negative breast cancer, alleles denoted as advantageous for survival correlated with the absence of alleles that protect against hypertension, leading to the observation that patients who experienced grade 3 to 4 hypertension experienced significantly longer overall survival (OS) than those patients who did not experience hypertension.¹⁹ A significant improvement in response and time to progression has also been reported for patients with metastatic progressive renal cell cancer who required antihypertensive medication during treatment with bevacizumab.²⁰ Early hypertension was also predictive of outcome among patients with pancreatic cancer²¹ and colorectal cancer.²²

This study presents results from an analysis of the clinical course of advanced NSCLC patients experiencing hypertension while receiving bevacizumab in combination with carboplatin and paclitaxel on the ECOG 4599 study, which demonstrated 2-month improvement in the median OS from 10.3 months to 12.3 months (hazard ratio [HR], 0.79; 95% CI, 0.67 to 0.92; $P = .003$) and a statistically significant increase in the rate of hypertension (carboplatin and paclitaxel [PC], 0.7% v PC and bevacizumab [PCB], 7.0%; $P < .001$) with the addition of bevacizumab. Hypertension was analyzed two different ways. The primary analysis classified patients as having high blood pressure (HBP) at the end of cycle 1 if their BP ever exceeded 150/100 or if their diastolic BP increased by more than 20 mmHg from baseline. The secondary analysis integrated all adverse events classified as hypertension. To the best of our knowledge, this is the first study to model HBP over time and among patients with NSCLC.

PATIENTS AND METHODS

ECOG 4599 was a phase III trial in which patients ($n = 878$) with advanced nonsquamous NSCLC were randomly assigned to first-line therapy of carboplatin (area under the concentration-time curve, 6 mg/mL $\times$ min, day 1) and paclitaxel (200 mg/m², day 1) with or without bevacizumab (15 mg/kg, day 1; PCB v PC) on a 21-day treatment cycle. Disease was assessed every 6 weeks, and patients who were assigned to PCB and had achieved stable disease or better (per Response Evaluation Criteria in Solid Tumors [RECIST]) following six cycles of treatment continued with maintenance bevacizumab alone until disease progression or toxicity (National Cancer Institute Common Terminology Criteria of Adverse Events [NCI CTCAE] v2.0). Eligible patients

($n = 850$) must have had stage IIIB disease with pleural or pericardial effusion or stage IV/recurrent NSCLC, ECOG performance status (PS) 0 or 1, and adequate bone marrow, hepatic, and renal function. All patients gave informed consent. Exclusion criteria for study registration were predominant squamous histology, history of brain metastases, gross hemoptysis (defined as bright red blood of 0.5 teaspoons or more), wound healing complications, or bleeding/thrombotic events. Patients with a history of hypertension must have been well controlled (BP $< 150/100$) and on a stable regimen of antihypertensive therapy. The primary end point of the study was OS. Secondary end points included PFS, response, and toxicity. The study was conducted in accordance with the Declaration of Helsinki, current US Food and Drug Administration Good Clinical Practices, and local institutional review board requirements.

Hypertension Substudy

The objective of this analysis was to study the clinical course of patients experiencing hypertension on ECOG 4599. Hypertension was assessed and analyzed two different ways. The primary analysis incorporated patient BP data, which were collected for all patients on PC and PCB before commencing each treatment cycle. Using the CTCAE as a guideline, HBP after one cycle of therapy was defined as BP $> 150/100$ at baseline or at the end of cycle 1 or an increase of > 20 mmHg in diastolic BP between these two time points. This is the main criteria for defining hypertension of at least grade 1. BP was also modeled as a time-dependent covariate over the entire course of treatment.

The secondary analysis integrated all hypertension events reported on the PCB arm as toxicity, regardless of treatment attribution or grade; the study protocol required that expected grade 3 to 5 events at least possibly attributable to treatment be reported. Because each toxicity form collects the date range during which toxicity occurred, sites were queried for the precise date of onset of hypertension for each patient for whom an event was reported. If a query was not resolved, the midpoint of the date range on the toxicity form was used as the date of onset of hypertension. If a patient's toxicity profile included more than one report of hypertension, only the first event was included in this analysis, since the secondary events were likely dependent on the initial event. This analysis does not present data on markers like *WNK1*, which is being assessed separately in an ECOG 4599 correlative study.

Statistical Methods

Baseline patient demographics, disease characteristics, and response were compared using Fisher's exact test. OS was defined as time interval in months from the landmark time to death from any cause. PFS was defined as the time interval in months from the landmark time to documented progression or death. Patients not experiencing an event were censored at the last date of follow-up for OS and the last date of disease assessment for PFS. Landmark analyses were estimated using the Kaplan-Meier method, and comparisons of the time-to-event distributions were made using the log-rank test.²³ Multivariable Cox proportional hazards models were used to estimate HRs for OS and PFS.²⁴ The cumulative incidence function of hypertension reported as an adverse event and adjusted for death as a competing event was constructed using the method of Kalbfleisch and Prentice.²⁵ All P values are two-sided, CIs are at the 95% level, and no adjustments have been made for multiple comparisons.

RESULTS

At a median follow-up of 55.2 months, 741 of 850 eligible patients (370 on the PCB arm, 371 on the PC arm) constituted the primary analysis population. Among the patients not included in this analysis were 106 patients missing BP measurements at baseline or at the end of cycle 1 and three other patients who died or progressed before the landmark time at the end of cycle 1. Table 1 displays the baseline patient demographics and disease characteristics by treatment arm and BP status after one cycle. The majority of patients were younger than age 65 years and presented with clearly recognized adenocarcinoma histology. Most patients did not have metastases to the liver, bone, or

Table 1. Distribution of Baseline Patient Demographics and Disease Characteristics by Blood Pressure Status After One Cycle of Therapy (n = 741)

Characteristic	PC				PCB			
	No HBP (n = 276)		HBP (n = 95)		No HBP (n = 263)		HBP (n = 107)	
	No.	%	No.	%	No.	%	No.	%
PS 1	166	60.1	51	53.7	162	61.6	55	51.4
Age ≥ 65 years	117	42.4	51	53.7	97	36.9	53	49.5
Adenocarcinoma	195	70.7	61	64.2	184	70.0	77	72.0
Female	109	39.5	40	42.1	130	49.4	54	50.5
Stage III/IV	249	90.2	86	90.5	229	87.1	89	83.2
Liver metastasis	55	19.9	11	11.6	52	19.8	24	22.4
Bone metastasis	91	33.0	35	36.8	79	30.0	26	24.3
Adrenal metastasis	51	18.5	13	13.7	36	13.7	13	12.1
Weight loss ≥ 5%	78	28.3	19	20.0	83	31.6	17	15.9
Prior RT	25	9.1	5	5.3	21	8.0	7	6.5

NOTE. Compared with the 109 patients not included in this analysis, these 741 patients had similar characteristics with the exception of a lower proportion of patients experiencing ≥ 5% weight loss ($P = .02$).

Abbreviations: PC, carboplatin and paclitaxel; PCB, PC + bevacizumab; HBP, high blood pressure; PS, performance status; RT, radiotherapy.

adrenal glands. A higher proportion of patients were males and had PS 1. On the PCB arm, patients presenting with HBP by the end of cycle 1 were significantly more likely to be at least 65 years of age ($P = .03$) or to have experienced < 5% weight loss in the previous 6 months ($P = .002$).

There was no difference in the baseline BP measurements between patients randomly assigned to PCB versus PC. The median and mean systolic and diastolic measurements (mmHg) from the start of each cycle of therapy for the first six cycles are displayed in Table 2. A total of 304 (35.8%) patients among the 850 eligible patients were known to have experienced HBP at least once during the course of therapy, but a higher proportion of patients experienced this on the PCB arm (187 [44.8%] of 417 patients on the PCB arm v 117 [27.0%] of 433 patients on the PC arm; $P < .0001$).

Figure 1 displays the results of the landmark analysis of OS measured from the end of cycle 1 by treatment arm and BP status. The median OS measured from the landmark time among those experiencing HBP on PCB was 15.9 months (95% CI, 13.4 to 20.3 months) and for those not experiencing HBP, it was 11.5 months (95% CI, 10.4 to 13.4 months). Among patients randomly assigned to PC alone, the

Fig 1. Landmark analysis of overall survival after one cycle of therapy. PC, carboplatin and paclitaxel; BP, blood pressure; PCB, PC + bevacizumab.

median OS times by BP status were similar (HBP, 10.3 months, 95% CI, 8.6 to 13.6 months; no HBP, 10.1 months, 95% CI, 8.8 to 12.1 months), and a test for the equality of these four OS distributions was statistically significant ($P = .0002$). Figure 2 presents the results of the landmark analysis of PFS, for which a median time of 7.0 months (95% CI, 5.6 to 8.6 months) was observed for patients experiencing HBP on PCB compared with 5.5 months (95% CI, 5.1 to 6.1 months) among patients not experiencing HBP on the same arm. Again, the PFS distributions of patients assigned to PC were similar: the median PFS for patients with HBP after 21 days was 3.6 months (95% CI, 3.2 to 5.0 months) versus 4.2 months (95% CI, 3.8 to 4.9 months) among those without HBP. The log-rank test of equality of these four PFS curves was also statistically significant ($P < .0001$).

Because it was of interest to obtain separate HRs for patients on PCB by BP status and to compare each of these groups with those patients on PC alone, multivariable Cox models were fitted. After adjusting for PS, adenocarcinoma histology, sex, weight loss ≥ 5%, and the presence of liver, bone, or adrenal metastases (age ≥ 65 years was not significant and fell out of the model), the resultant OS HR comparing those on PCB with HBP at the end of cycle 1 with those on PC alone was 0.68 (95% CI, 0.54 to 0.86; $P = .001$); similarly, comparing those on PCB without HBP after one cycle to those on PC alone, the adjusted OS HR was 0.84 (95% CI, 0.71 to 0.98; $P = .03$). The adjusted PFS HR comparing the PCB HBP group with the PC group

Table 2. Systolic and Diastolic Blood Pressure Measurements (mmHg) per Cycle

Start of Cycle	PC								PCB							
	Systolic				Diastolic				Systolic				Diastolic			
	Median	Range	Mean	SD	Median	Range	Mean	SD	Median	Range	Mean	SD	Median	Range	Mean	SD
1	130	90-192	130.2	18.5	74	46-108	74.2	10.2	130	84-192	129.3	17.6	74	42-110	74.3	10.4
2	129	80-194	130.0	18.8	75	50-102	75.0	9.9	133	86-194	134.8	18.8	80	46-128	78.8	11.3
3	130	80-198	131.5	19.0	76	45-102	75.6	10.7	134	76-210	136.1	19.2	80	50-112	79.7	10.6
4	130	85-222	130.6	18.6	74	48-110	74.7	10.4	135	90-212	136.6	20.1	80	47-114	80.0	11.8
5	128	92-199	129.4	18.4	76	50-100	75.4	9.8	135	90-188	136.6	18.4	80	57-110	79.4	10.4
6	128	82-203	128.2	18.1	76	40-100	75.0	10.2	136	90-200	137.1	18.8	80	48-112	80.7	10.6

Abbreviations: PC, carboplatin and paclitaxel; PCB, PC + bevacizumab; SD, standard deviation.

Fig 2. Landmark analysis of progression-free survival after one cycle of therapy. PC, carboplatin and paclitaxel; BP, blood pressure; PCB, PC + bevacizumab.

was 0.63 (95% CI, 0.50 to 0.78; $P < .0001$) and comparing those on PCB without HBP to those on PC gave an HR of 0.67 (95% CI, 0.57 to 0.79; $P < .0001$).

To address whether or not the outcomes for patients who experienced HBP on the PCB arm differed from the outcomes for patients who did not experience HBP on that arm, multivariable Cox models that included all prognostic variables mentioned above were fitted and adjusted for treatment in one model; treatment plus an indicator for being on PCB and experiencing HBP were fitted in another model. The likelihood ratio tests comparing these two models for OS and PFS were statistically significant ($P < .001$), indicating that patients on PCB who experienced HBP had significantly better outcomes than those on PCB who did not have HBP. To evaluate whether HBP is truly predictive, tests for a formal treatment by BP interaction were conducted and failed to reach significance because the study was underpowered for such a comparison.

Modeling HBP ($> 150/100$) as a time-varying covariate throughout one's entire duration of therapy yielded results similar to those obtained after just one cycle of therapy. In a model adjusted for the same prognostic variables as in the previous models, the OS HR comparing those with BP $> 150/100$ at any time point and on PCB to those on PC alone was 0.60 (95% CI, 0.43 to 0.81; $P = .001$); for those patients whose BP did not exceed 150/100, the HR was 0.86 (95% CI, 0.74 to 1.00; $P = .05$). Likewise, the adjusted PFS HRs were 0.54 (95% CI, 0.41 to 0.73; $P < .0001$) and 0.72 (95% CI, 0.62 to 0.84; $P < .001$), respectively. Analyses redefining HBP to be $> 140/90$ were conducted to test the sensitivity of these results to the change in criteria for HBP. Results were consistent with those presented here.

Regarding hypertension reported as an adverse event, 34 of the 417 patients randomly assigned to PCB experienced hypertension as toxicity. One of these events occurred more than 3 months post-treatment and was excluded from the analysis, leaving 33 hypertensive patients in this analysis. Thirty (90.9%) of these events were reported to be grade 3 hypertension, indicating that the patient required therapy or more intensive therapy than previously administered. There were two grade 2 events (recurrent or persistent BP $> 150/100$ if previously within normal limits or an asymptomatic transient increase by > 20 mmHg in diastolic BP). There was also one grade 4 event

Fig 3. Cumulative incidence of hypertensive toxicity over time adjusted for death as a competing risk. Curves represent the carboplatin, paclitaxel, and bevacizumab arm only since too few hypertension adverse events were reported on carboplatin and paclitaxel alone for a robust analysis to be conducted.

(hypertensive crisis). The date of onset of hypertension was retrieved for all but three patients. The number of hypertension events on the PC arm was too small ($n = 3$) for a robust analysis of this arm to be conducted. The median time to onset of hypertension toxicity on PCB was 1.94 months (range, 0.36 to 19.38 months), and the cumulative incidence of this adverse event was 6.2% (95% CI, 3.9% to 8.6%) at 6 months and 7.2% (95% CI, 4.7% to 9.7%) at 18 months. The estimated cumulative incidence function is displayed in Figure 3.

Landmark analyses measured from the median time to onset of hypertension (1.94 months) using the adverse event data to classify patients as hypertensive or not resulted in a nonstatistically significant trend toward superior outcomes for those patients who experienced hypertension as an adverse event. Among those on PCB, the median OS measured from the landmark time of 1.94 months among those experiencing hypertension before the landmark time was 14.0 months (95% CI, 8.8 to 44.6 months) compared with 11.3 months (95% CI, 10.1 to 13.3 months) among those not experiencing hypertension. There was also a nonstatistically significant trend for superior PFS among those who experienced hypertension; their median PFS from the landmark time was 8.0 months (95% CI, 6.0 to 16.2 months) compared with 4.5 months (95% CI, 4.2 to 5.0 months) among those who did not experience hypertension. A Cox model adjusted for onset of hypertensive toxicity as a time-varying covariate suggested a protective effect for hypertension (HR, 0.64; 95% CI, 0.43 to 0.96; $P = .03$), but this result did not remain statistically significant in an adjusted model. Hypertension was not a univariate predictor of PFS (HR, 0.83; 95% CI, 0.57 to 1.21; $P = .32$).

DISCUSSION

Several studies support the hypothesis that the onset of hypertension during treatment with bevacizumab correlates with antitumor activity and superior outcome, but to the best of our knowledge, this study is

the first to address the analysis with the appropriate statistical methods. Comparisons of time-to-event data measured from baseline and made on the basis of treatment outcome variables, such as hypertension, are inherently biased because the classification of hypertension requires that patients survive long enough for hypertension to be observed. Therefore, patients who die soon after random assignment would almost always be classified as nonhypertensive in this analysis, making the resultant Kaplan-Meier estimates for this group unfavorably biased and the log-rank test invalid.²⁶⁻³⁰ The appropriate analyses for these types of data implement landmark analyses and models that consider hypertension a time-varying covariate.

These results demonstrate that hypertension may serve as a predictor of improved outcome via enhanced VEGF inhibition and that adverse events tend to occur soon after the start of treatment. Although results stemming from the analysis of the toxicity data generally did not reach statistical significance, models adjusted for HBP, which was measured at every treatment cycle, suggest a strong association with outcome. An explanation for this discrepancy may be the under-reporting of grades 1 and 2 toxicities, defined as BP > 150/100 or an increase of > 20 mmHg in diastolic BP if it was previously with normal limits and did not require treatment. The ECOG 4599 protocol did not require that grades 1 or 2 hypertension be reported; this serves as a reminder that one must not rely heavily on toxicity reporting as an accurate and complete profile of a drug's adverse effects. BP is also a less subjective measurement than toxicity, which must have been perceived as unexpected or at least possibly attributable to treatment in order to be reported.

Information regarding comorbidities, concomitant medications, and antihypertensive therapy was not collected on this trial and restricts the analysis to what was done here. Although retrospective analyses present their own limitations, the results emphasize a need for prospective evaluation of hypertension as a feasible and affordable biomarker for improved outcome. Supporting risk stratification based on genotyping and a genetic susceptibility to hypertension, Frey et al³¹ reported an association between *WNK1*, which regulates sodium reabsorption in the distal nephron of the kidneys, and bevacizumab-induced hypertension. Because the degree of hypertension increases as the dose of the bevacizumab increases,^{32,33} some have suggested dose titration until BP becomes elevated. Others have suggested more rigorous toxicity monitoring and prophylactic therapy for hypertension.³⁴

Because hypertension is a risk factor for coronary heart disease, stroke, heart failure, and end-stage renal disease, this adverse effect must be managed to prevent the onset of cardiovascular events while on treatment with bevacizumab. The incidence of bevacizumab-associated hypertension depends on the dosing schedule and other factors, such as patient age and comorbidities, which may have an impact on why a clear recommendation for an antihypertensive

regimen for patients receiving bevacizumab has not been made.³⁵ Regardless, hypertension is generally well managed with oral antihypertensives such as angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers.¹⁴ Hypertension does not necessitate a dose reduction of bevacizumab because reducing tumor burden remains the top priority, the risks of which outweigh the risks of hypertension.³⁶

In summary, this study demonstrates that the onset of HBP during treatment with PCB may result in improved outcomes among patients with advanced nonsquamous NSCLC. Further studies of the downstream effects of VEGF suppression and hypertension are needed to identify patients who are susceptible to bevacizumab-induced hypertension.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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