Clinical Cancer Research

Diastolic Blood Pressure as a Biomarker of Axitinib Efficacy in Solid Tumors

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Abstract

Purpose: To evaluate if diastolic blood pressure (dBP) ≥90 mm Hg during axitinib treatment is a marker of efficacy.

Experimental Design: The relationship between dBP ≥90 mm Hg and efficacy was retrospectively explored across 5 phase II studies of single-agent axitinib for the treatment of 4 different tumor types. All patients had baseline BP ≤140/90 mm Hg and were stratified into 2 groups based on in-clinic BP measurements after initiating therapy: those with dBP <90 mm Hg throughout therapy and those with at least 1 dBP ≥90 mm Hg. Median overall survival (mOS), median progression-free survival (mPFS), objective response rate (ORR), and adverse events were evaluated by dBP group in individual and pooled analyses.

Results: Two-hundred thirty patients were evaluated. Patients with dBP ≥90 mm Hg had a significantly lower relative risk of death than those with dBP <90 mm Hg [adjusted HR (95% CI) = 0.55 (0.39, 0.77); $P < 0.001$]. The relative risk of progression was also lower in patients with dBP ≥90 mm Hg [HR (95% CI) = 0.76 (0.54, 1.06), $P = 0.107$], and ORR was significantly higher (43.9% vs. 12.0%; $P < 0.001$). In an 8-week landmark analysis, mOS (25.8 vs. 14.9 months) and mPFS (10.2 vs. 7.1 months) were greater for patients in the ≥90 mm Hg group. Adverse events were similar between groups.

Conclusions: Axitinib efficacy correlated with dBP ≥90 mm Hg. Further investigation of dBP as a predictive biomarker of efficacy in patients receiving axitinib is warranted. *Clin Cancer Res; 17(11); 3841–9.* ©*2011 AACR.*

Introduction

VEGF-targeted agents have contributed to increased success in the treatment of cancer (1), but not all patients benefit from therapy and the prediction of individual benefit remains problematic. The identification of a valid, inexpensive, and easily measurable predictive biomarker of efficacy is of great interest. Numerous antiangiogenic biomarkers have been studied; however, to date no validated biomarker exists for selecting patients for antiangiogenic therapy (1).

The occurrence of increased blood pressure (BP) with the use of VEGF-targeted agents is widely reported (2, 3). This effect is usually manageable with dose modification and/or antihypertensive therapy (3). Systematic meta-analyses report a significantly increased risk of hypertension in cancer patients treated with bevacizumab (4), sunitinib (5), or sorafenib (6) compared with patients not receiving antiangiogenic therapy. This effect may be attributed to disruption of VEGF–VEGF receptor (VEGFR) signaling. Recent studies suggest that inhibition of VEGFR suppresses nitric oxide production, causing increased vascular resistance and BP. Further, endothelial cell death induces vascular rarefaction, reduces vascular distensibility, and alters endothelin function (2).

Axitinib is an oral, potent, and selective inhibitor of VEGFR-1, -2, and -3 currently in phase III development for metastatic renal cell carcinoma (mRCC). A phase I dose-finding study suggested a relationship between axitinib exposure and BP (7). Data from patients with mRCC indicated that BP increased early during the course of treatment with axitinib (within 1 week in 25% of patients; ref. 8). Preclinical data show that axitinib rapidly inhibits downstream signaling via the endothelial nitric oxide synthase/protein kinase B pathway implicated in normal vascular homeostasis, suggesting elevated BP during axitinib treatment is related to its inhibitory effects on VEGFR-2 (9). On the basis of these data, it was hypothesized that drug-induced BP elevation may be an early indicator of drug activity at the desired molecular target, serving as a

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Translational Relevance

Antiangiogenic agents are associated with elevated blood pressure (BP), and it has been hypothesized that drug-induced BP elevation may be associated with clinical outcome. Axitinib is an oral, potent, and selective inhibitor of VEGFR-1, -2, and -3 with single-agent activity in a variety of tumor types. This analysis investigated the utility of diastolic BP (dBP) ≥90 mm Hg as a biomarker of efficacy across 5 phase II single-agent axitinib studies for the treatment of 4 different tumor types. In pooled and individual analyses, the occurrence of an on-treatment dBP measurement ≥90 mm Hg was associated with improved outcomes compared with dBP <90 mm Hg throughout therapy. These data support further evaluation of dBP as a biomarker of clinical outcome in patients receiving axitinib.

biomarker of VEGF pathway inhibition, and thus may be associated with clinical outcome. This retrospective analysis explored the utility of diastolic BP (dBP) ≥90 mm Hg as a clinical biomarker of axitinib efficacy across 5 independent phase II single-agent studies.

Materials and Methods

Patient population and study design

Five phase II multicenter trials evaluating the safety and efficacy of axitinib in multiple solid tumors, including mRCC (2 trials; refs. 8, 10), non–small cell lung cancer (NSCLC; ref. 11), melanoma (Fruehauf and colleagues, manuscript in preparation), and thyroid cancer (12) were analyzed (Table 1).

Briefly, eligibility criteria common to all 5 studies included patients aged ≥18 years with histologically or cytologically confirmed malignancy; no preexisting uncontrolled hypertension, defined by baseline BP >140/90 mm Hg (antihypertensive medications permitted); an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; and adequate organ function. For these analyses, dBP was selected because it is less labile than systolic BP (sBP), and dBP ≥90 mm Hg is a commonly used criterion for hypertension (13).

These trials were carried out in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, applicable local regulatory requirements and laws, and individual protocols approved by their respective institutional review boards. All patients provided written informed consent.

Treatment

All patients received starting doses of axitinib 5 mg twice daily (BID) as single-agent therapy in repeated 4-week cycles. Axitinib dose reductions and temporary interruptions were permitted to manage adverse events (AE). Patients without grade 3/4 treatment-related AEs and with BP <150/90 mm Hg for consecutive 2-week periods were eligible for dose titration to 7 mg BID and then to a maximum of 10 mg BID. Patients who developed sBP >150 mm Hg or dBP >100 mm Hg (2 BP measurements separated by ≥1 hour) were administered new or additional antihypertensive therapy or had the axitinib dose decreased by 1 level if already receiving maximal hypertensive therapy. For patients developing sBP >160 mm Hg or dBP >105 mm Hg (2 BP measurements separated by ≥1 hour), axitinib dosing was interrupted until BP was <150/100 mm Hg, and then resumed with the axitinib dose decreased by 1 level. In cases of persistent or recurrent hypertension following axitinib dose reduction, the axitinib dose was decreased by another level or withheld.

Assessments

Patients underwent physical examinations and laboratory testing at baseline and every 4 weeks thereafter. Patients measured their own BP at least daily and were instructed to contact their physician immediately for sBP >150 mm Hg or dBP >100 mm Hg. For the sorafenib-refractory mRCC study, in-clinic BP measurements were obtained every 2 weeks for 6 visits and then every 4 weeks. For all other studies, in-clinic BP measurements were obtained every 4 weeks. Measurements of BP were taken with patients seated and resting for 5 minutes.

On the basis of in-clinic BP measurements, patients were retrospectively stratified into 2 groups after initiation of axitinib therapy: patients with dBP measurements <90 mm Hg throughout the study (<90 group), and patients with at least 1 dBP ≥90 mm Hg at any time during the study (≥90 group). For patients with more than 1 dBP ≥90 mm Hg, the first dBP measurement ≥90 mm Hg was used for these analyses. Median overall survival (OS), median progression-free survival (PFS), objective response rate (ORR), and AEs were evaluated by dBP group. Home BP measurements were not collected prospectively and were not available for analysis.

Safety and tolerability were evaluated by physical examination, laboratory tests, and AE assessment according to the National Cancer Institute Common Terminology for Adverse Events (NCI CTAE), version 3.0 (14). Tumor responses were assessed at baseline and every 8 weeks thereafter according to Response Evaluation Criteria and Solid Tumors (RECIST) 1.0 (15).

Statistical analysis

Analyses of hazard ratios were conducted using a Cox proportional hazards model (16), with the first onset of dBP ≥90 mm Hg obtained in the clinic treated as a time-dependent covariate. Thus, a given patient is not accounted for in the dBP ≥90 mm Hg risk set until the first in-clinic measurement ≥90 mm Hg is observed. This is in contrast to a fixed covariate Cox proportional hazards model in which a patient would be assigned to the dBP ≥90 mm Hg risk set for the duration of their time on study. This method controls for potential bias

Table 1. Summary of axitinib clinical trials included in the diastolic blood pressure–efficacy combined analyses

	Main trial, *N*	dBP-efficacy analyses, *n*	Patient population	End points	Major findings
Fruehauf and colleagues[a]	32	29	Metastatic melanoma	Primary: ORR Secondary: PFS, DR, OS, PK, safety, biomarkers	ORR 18.8% (95% CI 7.2–36.4) Median DR 5.9 mo (95% CI 5.0–17.0) Median PFS 3.9 mo (95% CI 2.3–6.7) Median OS 6.6 mo (95% CI 5.2–9.0) Common all-causality AEs: fatigue, hypertension, nausea, diarrhea, hoarseness; Grade $\geq$3 hypertension 9.4% ($n = 3$)
Rini and colleagues (10)	62	61	Sorafenib-refractory metastatic renal cell cancer	Primary: ORR Secondary: DR, PFS, OS, population PK safety, patient-reported outcomes	ORR (overall) 22.6% (14/62) Median PFS (overall) 7.4 mo (95% CI 6.7–11.0) Median OS (overall) 13.6 mo (95% CI 8.4–18.8) Most common grade 3 AEs were hand–foot syndrome (16.1%), fatigue (16.1%), hypertension (14.5%), diarrhea (9.7%)
Schiller and colleagues (11)	32	30	Advanced non–small cell lung cancer	Primary: ORR Secondary: DR, PFS, OS, safety/tolerability	ORR 9% Median DR 8.3 mo (95% CI 5.9–10.6) Median PFS 4.9 mo (95% CI 3.6–7.0) Median OS 14.8 mo (95% CI 10.7-NR) Most common grade 3 AEs: fatigue (22%), hypertension (9%), diarrhea (3%)
Rixe and colleagues (8)	52	51	Cytokine-refractory metastatic renal cell cancer	Primary: ORR Secondary: DR, TTP, OS, PK, safety, patient-reported HRQoL	ORR 44.2% (95% CI 30.5–58.7) Median DR 23 mo (95% CI 20.9-NE) Median TTP 15.7 mo (95% CI 8.4–23.4) Median OS 29.9 mo (95% CI 20.3-NE) Treatment-related AEs included diarrhea, hypertension, fatigue, nausea, hoarseness
Cohen and colleagues (12)	60	59	Advanced thyroid cancer	Primary: ORR Secondary: PFS, DR, OS, safety, biomarkers	ORR 30% (95% CI 18.9–43.2) Median PFS 18.1 mo (95% CI 12.1-NE) Grade $\geq$3 hypertension 12% ($n = 7$)
All studies combined	238	230	–	–	–

Abbreviations: HRQoL, health-related quality of life; NE, not estimable; NR, not reached; PK, pharmacokinetics; TTP, time to progression.

[a]Fruehauf and colleagues, manuscript in preparation.

Table 2. Baseline characteristics in patients with and without dBP ≥90 mm Hg

	dBP group, mm Hg		
	<90 *n* = 100 *n* (%)[a]	≥90 *n* = 130 *n* (%)[a]	*P*
Median age, y (range)	60 (26–83)	60 (31–86)	0.736
Gender, male	63 (63)	87 (67)	0.536
ECOG PS			
0	38 (40)	71 (55)	0.025
1	58 (60)	59 (45)	
Antihypertensive therapy at baseline			0.452
Yes	45 (45)	65 (50)	
No	55 (55)	65 (50)	
Median number of antihypertensive therapies at baseline			0.304
1	22 (22)	24 (18)	
2	12 (12)	28 (22)	
>2	11 (11)	13 (10)	
Median dBP at baseline, mm Hg	70	76	<0.001
In patients receiving antihypertensive therapy at baseline	70	76	0.004
In patients not receiving antihypertensive therapy at baseline	70	78	<0.001
Median sBP at baseline, mm Hg	120	128	<0.001
In patients receiving antihypertensive therapy at baseline	125	130	0.125
In patients not receiving antihypertensive therapy at baseline	117	124.5	<0.001
Median time to first dBP ≥90 mm Hg, mo (range)	–	1.0 (0.03–24.2)	N/A
Axitinib dose at the time of first dBP ≥90 mm Hg[b]			
<10 mg daily	–	25 (19)	N/A
=10 mg daily (=5 mg BID)	–	84 (65)	
>10 mg daily	–	20 (16)	
Initiated antihypertensive therapy following initiation of axitinib therapy[c]	12 (22)	45 (69)	<0.001
Patients receiving axitinib dose titration ≥14 mg daily	20 (20)	33 (25)	0.336

Abbreviation: N/A, not applicable.
[a]Unless otherwise noted.
[b]Data not available for 1 patient.
[c]Among patients not receiving antihypertensive therapy at baseline.

resulting from patients living longer and, consequently, having a greater opportunity for dBP ≥90 mm Hg due to an increased number of BP measurements (17). A landmark analysis (18) was conducted using the maximum dBP achieved by week 8 (allowing for 2 in-clinic BP measurements) to stratify patients into the dBP <90 or ≥90 groups, and assessed OS and PFS from that point forward. All patients dying or progressing, according to the particular end point, prior to the 8-week landmark were excluded from the analyses. Medians of OS and PFS were estimated with Kaplan–Meier methods using time from the 8-week landmark. Response rates were compared using Fisher's exact test. All statistical tests were 2-sided at a 5% level of significance. Statistical analyses were carried out using SAS software (versions 8.2 and 9.1; SAS Institute Inc.).

Results

Patient characteristics

Of the 238 patients who received axitinib across the 5 phase II trials, 230 were included in these analyses. Eight patients were not included because postbaseline dBP values were not available due to early study withdrawal. Demographic variables, including median age, gender, baseline PS, and baseline median BP, were similar across the 5 trials. At baseline, median dBP (range, 70–80 mm Hg) and median sBP (range, 111–130 mm Hg) were comparable across the individual trials.

Of the 230 patients analyzed by stratification group (Table 2), 43% ($n = 100$) were in the <90 group and 57% ($n = 130$) in the ≥90 group. Median age and gender were similar between these 2 groups. Median dBP at

Table 3. Overall and progression-free survival estimates from landmark analysis and ORRs in the dBP <90 and ≥90 mm Hg groups

Study tumor type	n[b]	Patients by dBP (mm Hg) group					
		Median overall survival from landmark, mo		Median progression-free survival from landmark, mo		Objective response rate[a], %	
		<90	≥90	<90	≥90	<90	≥90
Melanoma (Fruehauf and colleagues)[c]	29	4.6	8.7	2.3	5.9	20.0	21.4
Sorafenib-refractory mRCC (10)	61	11.6	14.7	5.8	5.7	9.7	36.7
NSCLC (11)	30	12.8	NR	5.0	2.2	5.9	15.4
Cytokine-refractory mRCC (8)	51	18.4	28.1	7.9	21.4	10.5	65.6
Thyroid cancer (12)	59	NR	29.2	14.5	13.1	16.7	48.8
Pooled analysis	**230**	**14.9**	**25.8**	**7.1**	**10.2**	**12.0**	**43.9**

Abbreviation: NR, not reached.

[a]Proportion of patients who experienced complete or partial responses.

[b]Number of patients having dBP measurements meeting criteria for inclusion in dBP analyses.

[c]Fruehauf and colleagues, manuscript in preparation.

baseline was significantly higher in the ≥90 group than the <90 group ($P < 0.001$) irrespective of antihypertensive therapy use at baseline. In the ≥90 group, 65 patients (50%) and 87 patients (67%) exhibited dBP ≥90 at weeks 4 and 8, respectively. More than half of patients in the ≥90 group had a maximum dBP measurement ≥94 mm Hg.

Diastolic blood pressure and efficacy relationships

In a pooled analysis of OS (events, $n = 140$), there was a significantly lower relative risk of death for patients in the ≥90 group compared with those in the <90 group [HR (95% CI) = 0.55 (0.39, 0.77); $P < 0.001$; Table 3; Fig. 1]. The pooled analysis showed a 45% reduction in the risk of death for patients in the ≥90 group (Table 4). Multivariate analyses, including dBP, baseline PS, dose level, and use of antihypertensive medication in the model, revealed that dBP was an independent predictor of OS, with an HR of 0.676 (95% CI 0.470–0.972; $P = 0.036$) in favor of the ≥90 group.

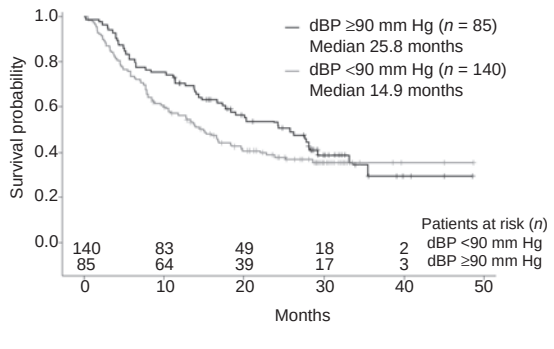

Figure 1. Landmark analysis of overall survival in patients with and without dBP ≥90 mm Hg with landmark at 8 weeks.

Similar trends were observed for PFS and ORR (Tables 3, 4). In the pooled analysis, PFS was 3.1 months longer for patients in the ≥90 group compared with the <90 group. Similarly, in the pooled analysis, ORR was significantly higher in the ≥90 group compared with the <90 group (43.9% vs. 12.0%; $P < 0.001$). The greatest tumor response difference by dBP group was observed in patients with cytokine-refractory mRCC (65.6% vs. 10.5%, ≥90 vs. <90 groups, respectively; $P < 0.001$). In all 5 individual trials, the ORR was numerically higher in patients in the ≥90 group compared with the <90 group.

A landmark analysis for OS and PFS measured from 8 weeks after initiation of axitinib therapy supported the overall analyses. For patients in the ≥90 group compared with the <90 group, respectively, the median OS [25.8 vs. 14.9 months; HR (95% CI) = 0.77 (0.54, 1.10); $P = 0.150$] and median PFS [10.2 vs. 7.1 months; HR (95% CI) = 0.80 (0.57, 1.14); $P = 0.215$] were numerically greater. For the 2 RCC studies, median PFS was significantly longer for patients in the ≥90 group compared with the <90 group [16.5 vs. 6.4 months; HR (95% CI) = 0.53 (0.31, 0.90); $P = 0.019$], and median OS was numerically greater [25.8 vs. 13.9 months; HR (95% CI) = 0.74 (0.45, 1.21); $P = 0.228$]. Per this landmark method, patients who died ($n = 5$) or progressed ($n = 47$) prior to 8 weeks are excluded, and thus statistical power is lost compared with the time-dependent Cox model covariate analyses.

Safety and tolerability

Pooled data for single-agent axitinib treatment suggest that grade 3/4 AEs were largely similar between the 2 dBP groups, with the exception of hypertension, hand–foot

Table 4. Statistical results for pooled analyses of efficacy

Efficacy outcome	dBP group, mm Hg		Adjusted hazard ratio (95% CI)	*P*
	<90	≥90		
Median overall survival, mo[a]	14.9	25.8	0.55 (0.39–0.77)	<0.001
Median progression-free survival, mo[a]	7.1	10.2	0.76 (0.54–1.06)	0.107
Objective response rate, %	12.0	43.9	–	<0.001

[a]HRs and *P* values are from Cox model using onset of dBP ≥90 mm Hg as a time-dependent covariate.

syndrome, and arthralgia, which were reported more often in the ≥90 group compared with the <90 group (Table 5). In the <90 group, 7 patients had an AE of hypertension: 2 patients had evidence of hypertension as defined by sBP; the remaining 5 patients may have had home BP measurements that prompted an AE report of hypertension or changes in the in-clinic BP measurement from baseline that were considered hypertension by the investigator but did not meet the dBP ≥90 mm Hg threshold for these analyses.

Discussion

In this exploratory retrospective pooled evaluation of 5 phase II axitinib clinical studies, the occurrence of an on-treatment dBP measurement ≥90 mm Hg was associated with a longer median OS and PFS, and a higher ORR compared with dBP <90 mm Hg throughout therapy. These relationships were consistent across multiple tumor types for pooled data and were in agreement with individual studies for each efficacy end point. Among the individual trials, this relationship was most significant for patients with mRCC. The association between dBP response and outcome may indicate increased sensitivity to VEGF inhibition in RCC patients that developed dBP ≥90 mm Hg on study. Noting the inherent limitations of subset analyses, the relationship of dBP with axitinib response and clinical outcome may be less strong in non-RCC tumor types due to their reduced dependence on the VEGF pathway.

Previous studies have investigated hypertension as a predictive biomarker of the effectiveness of antiangiogenic therapy. Retrospective analyses evaluating the relationship between hypertension and outcome in patients treated with sunitinib, bevacizumab, or sorafenib report a similar relationship to that observed here for axitinib (19–26). A recent study, which used the same statistical analyses employed here, found that patients with mRCC who developed hypertension (defined as dBP ≥90 mm Hg or sBP ≥140 mm Hg) while receiving sunitinib had significantly longer OS than those with BP <90/140 mm Hg ($P < 0.0001$; ref. 19). In the phase III trial of carboplatin and paclitaxel with or without bevacizumab for advanced NSCLC (ECOG 4599 trial), patients receiving bevacizumab and experiencing high BP (defined as 1 or more BP reading >150/100 mm Hg or an increase >20 mm Hg from baseline) had a longer median OS from the end of the first treatment cycle compared with patients without high BP (15.9 vs. 11.5 months, respectively; ref. 22). Patients receiving bevacizumab and experiencing hypertension as an AE had a longer median OS from the median time to onset of hypertension than those not experiencing hypertension (14.0 vs. 11.3 months, respectively; ref. 22). Similar relationships were reported in patients receiving bevacizumab with metastatic breast cancer (ECOG 2100; ref. 23), pancreatic cancer (24), mRCC (21, 25), and colorectal cancer (26). However, in the phase III AVOREN trial of bevacizumab combined with interferon alfa-2a for mRCC (27), grade ≥2 hypertension was not associated with improvements in PFS; this analysis may have been limited by the use of common toxicity criteria (CTC) grading, not actual BP measurements, and short follow-up. Analysis of a similar trial of bevacizumab combined with interferon alfa-2a for mRCC (CALGB 90206) supports the hypothesis generated here of improved clinical outcome in patients developing hypertension during therapy (28). The present evaluation is consistent with these data, but is distinct in that it included a large number of patients with cancers of diverse histologies.

In analyses correlating BP with outcome, there is no standardized method for categorizing patients with increased BP or hypertension during antiangiogenic therapy. Studies have used different criteria to define elevated BP, including: ≥140/90 mm Hg (19), >150/100 mm Hg (22, 25), an increase in dBP >20 mm Hg from baseline (22), or grading of hypertension according to NCI CTCAE or NCI CTC (21, 22, 24, 26). These methods have inherent limitations. Studies using NCI CTCAE version 2.0 or 3.0 grading system, which defines hypertension as >150/100 mm Hg or an increase in dBP >20 mm Hg, may underestimate the number of patients with increased BP, as those with BP 140–150/90–100 mm Hg would not be included (6). Moreover, studies using the NCI CTCAE grading system may apply inconsistent definitions of grade 2 and 3 hypertension, which are not mutually exclusive and may be subject to interpretation (6). The threshold of dBP ≥90 mm Hg employed here is commonly used in clinical practice for assessing clinically relevant changes in BP (13, 29) and was also used to assess hypertension as a biomarker of sunitinib efficacy (19). A limitation of this threshold was that patients with a dBP equal to 90 mm Hg at baseline were included (<90 group, 3%; ≥90 group, 7%); thus, dBP of 90 mm Hg in the ≥90 group cannot be definitively characterized as

Table 5. All grade and grade 3/4 nonhematological AEs of clinical interest, regardless of causality: pooled analysis

Event	No. of patients by dBP group, mm Hg			
	All grades		Grade 3/4	
	<90 *n* (%)	≥90 *n* (%)	<90 *n* (%)	≥90 *n* (%)
Fatigue	69 (69)	107 (82)	18 (18)	19 (15)
Hypertension	30 (30)	97 (75)	7 (7)	31 (24)
Diarrhea	47 (47)	93 (72)	9 (9)	14 (11)
Nausea	46 (46)	76 (58)	3 (3)	3 (2)
Anorexia	42 (42)	64 (49)	4 (4)	2 (2)
Weight loss	27 (27)	55 (42)		
Constipation	29 (29)	50 (38)		
Headache	24 (24)	50 (38)	4 (4)	3 (2)
Cough	18 (18)	48 (37)		
Hoarseness	20 (20)	46 (35)		
Vomiting	26 (26)	39 (30)	3 (3)	2 (2)
Insomnia	12 (12)	36 (28)		
Mucositis	16 (16)	34 (26)		
Dry skin	11 (11)	33 (25)		
Shortness of breath	18 (18)	33 (25)		
Hand–foot syndrome/palmar-plantar erythrodysesthesia syndrome	9 (9)	32 (25)	1 (1)	14 (11)
Depression	16 (16)	25 (19)		
Heartburn	11 (11)	25 (19)		
Hypothyroidism	17 (17)	25 (19)		
Stomatitis	16 (16)	25 (19)	2 (2)	3 (2)
Arthralgia	7 (7)	24 (18)	0	5 (4)
Rash	4 (4)	24 (18)		
Shoulder pain	5 (5)	24 (18)		
Proteinuria	12 (12)	23 (18)		
Dyspnea	21 (21)	22 (17)	6 (6)	10 (8)
Dehydration	12 (12)	20 (15)		
Asthenia/weakness	5 (5)	5 (4)	1 (1)	1 (1)

treatment-induced for these few patients, Furthermore, mean changes in dBP from baseline were not assessed; thus, patients may have developed increased dBP without reaching the ≥90 mm Hg threshold, and the incidence of drug-induced BP elevations may have been underestimated. In addition, as BP was significantly higher in the ≥90 group prior to initiation of axitinib therapy, the possibility that baseline BP is predictive of clinical outcome during therapy cannot be excluded. The inconsistency in definitions used to assess hypertension in patients receiving antiangiogenic therapy precludes direct comparisons among published studies. Despite differences in the methodologies used and their associated limitations, the results presented here and in prior analyses indicate that elevated BP during treatment with angiogenesis inhibitors correlates with improved outcomes. The recently revised NCI CTCAE grading system (version 4.0; ref. 30) uses guidelines similar to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (29) and includes BP ≥140/90 mm Hg in the definition of hypertension, and may therefore be useful for future studies of hypertension as a biomarker of antiangiogenic therapy.

To date, all analyses of BP or hypertension as a biomarker of antiangiogenic therapy have been retrospective. While the approaches used here are appropriate and consistent with those employed in similar analyses (19, 22), prospective clinical studies evaluating the relationship between dBP and clinical outcome would be favored. A recent study employing ambulatory BP monitoring (ABPM) in patients receiving sorafenib reported increases in BP within 24 hours of treatment, although changes in BP were highly variable among patients (31). This method would allow for continuous assessments of BP changes during treatment with angiogenesis inhibitors and subsequent correlation with survival.

Other potential limitations of this analysis include heterogeneity in patients and tumor types, possible imbalances within each study for prognostic factors between dBP subgroups, and retrospective interpretation of data from small, single-arm, phase II studies. Evaluation of BP in larger clinical studies is needed to determine if dBP ≥90 mm Hg during axitinib therapy is a bona fide marker of clinical outcome. These analyses are ongoing in clinical trials of axitinib for a variety of tumor types, including the phase III trial comparing axitinib with sorafenib as second-line treatment for mRCC. In addition, the present analysis looked only at dBP changes and not changes in systolic BP due to less lability in measurement. It is possible that systolic BP may also be a potential biomarker, and such data is being gathered in ongoing trials with axitinib.

Comparisons of survival between treatment response groups are inherently biased, as responders, patients in the ≥90 group in this study, must live long enough for the response to be observed (17, 19, 22). Two valid approaches (17, 19, 22) were used in the current study to minimize this inherent bias. First, the onset of dBP ≥90 mm Hg was treated as a time-dependent variable for modeling OS, PFS, and ORR measured from baseline, which takes into account the temporal relationship between dBP and outcome. For each event, the risk sets are redefined, i.e., a patient will move into the ≥90 group if dBP ≥90 mm Hg was observed in that patient by the time of that event. A patient's exposure status is thus allowed to vary over time. A multivariate model incorporating baseline PS, antihypertensive use, and dose level in addition to the time-dependent dBP covariate also showed dBP to be an independent predictor of OS. Still, it is not possible to completely remove the possible confounding of dosing and antihypertensive therapies with dBP elevation and their effect on OS. Second, a landmark analysis was conducted that evaluated OS and PFS from week 8, based on the maximum dBP achieved at that time. This method corrects for bias by fixing the time-point for determination of dBP ≥90 mm Hg and observing OS or PFS events from that point forward. In the landmark analysis, median OS and PFS were longer for patients in the ≥90 group compared with the <90 group but this difference did not reach statistical significance. Some statistical power is lost with this method, as patients who died or progressed are excluded, regardless of their respective BP response. The number of patients evaluated here was small compared with similar studies that reported significantly improved outcomes in patients receiving sunitinib or bevacizumab and experiencing hypertension during therapy by landmark analyses (19, 22). Evaluation of a larger population with sufficient statistical power, such as the phase III trial of axitinib for second-line mRCC cited above, is needed to more fully evaluate dBP ≥90 mm Hg as marker of efficacy during axitinib therapy using landmark analyses.

Initial observations in an axitinib phase I trial (7) suggested that the incidence and severity of elevated BP was dose dependent. However, preliminary pharmacokinetic–pharmacodynamic evaluations in mRCC patients suggested dBP ≥90 mm Hg with axitinib therapy was an independent predictor of clinical efficacy and not merely a reflection of higher axitinib drug concentrations (32). Nonetheless, increases in BP during axitinib treatment may be related, in part, to axitinib exposure and may not occur in patients receiving suboptimal doses. Pharmacokinetic data are not available for all patients in the present analysis to fully evaluate this hypothesis. Observations in the RCC studies (8, 10) suggested that upward dose titration among patients with BP <150/90 mm Hg and without significant toxicity may translate into improved clinical outcomes. Thus, individualized patient dose titration may be important for optimal clinical response. Prospective testing of this hypothesis is ongoing and will be required before these data can be useful to guide individual patient therapy decisions (33).

In these 5 trials in different tumor types, axitinib was well tolerated. Patients in the ≥90 group had an increased incidence of grade 3/4 hypertension, hand–foot syndrome, and arthralgia, all of which are commonly reported AEs with VEGF/VEGFR inhibitors. Treatment-induced BP elevation secondary to VEGF/VEGFR inhibitors is generally asymptomatic and manageable with standard antihypertensive therapy or dose reductions (3). The use of VEGF-targeted agents earlier in treatment paradigms may also require early and appropriate BP management to ensure patients receive optimal dosage of therapy, while minimizing hypertension-related sequelae. Our findings suggest that patients in the ≥90 group had a longer median OS, irrespective of antihypertensive use at baseline or during the trial, compared with patients in the <90 group. Thus, the use of antihypertensive medication did not appear to negate the clinical benefit of dBP ≥90 mm Hg.

Despite substantial efforts, identification of a robust and reliable biomarker for antiangiogenic agents has proved elusive. Serial measurements of dBP are convenient and may be useful once therapy is started. Pooled and individual analyses presented here suggest that patients treated with axitinib had a dBP ≥90 mm Hg early during therapy and that dBP ≥90 mm Hg was associated with clinical improvements across multiple tumor types. This retrospective pooled evaluation suggests that dBP may be a simple, reliable, and inexpensive predictive biomarker of efficacy for an angiogenesis inhibitor. On the basis of these findings, further investigation of dBP as a biomarker of axitinib efficacy is warranted. An ongoing prospective clinical trial of axitinib in patients with mRCC is assessing ambulatory blood pressure and evaluating the relationship between BP and clinical outcome (32).

Disclosure of Potential Conflicts of Interest

B.I. Rini received a major commercial research grant and J.H. Schiller received a minor commercial research grant from Pfizer Inc.; both are consultant with Pfizer Inc. A.D. Ricart, S. Kim, B. Rosbrook, and A.J. Olszanski have ownership interest in Pfizer Stock.

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