

Ambulatory Monitoring Detects Sorafenib-Induced Blood Pressure Elevations on the First Day of Treatment

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Abstract Purpose: Hypertension is a mechanism-based toxicity of sorafenib and other cancer therapeutics that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. This prospective, single-center, cohort study characterized ambulatory blood pressure monitoring as an early pharmacodynamic biomarker of VEGF signaling pathway inhibition by sorafenib.

Experimental Design: Fifty-four normotensive advanced cancer patients underwent 24-hour ambulatory blood pressure monitoring before and between days 6 and 10 of sorafenib therapy. After blood pressure changes were detected among the first cohort within 10 days, ambulatory blood pressure monitoring was done during the first 24 hours of treatment for the second cohort.

Results: For the entire patient population, the blood pressure increase [mean systolic, +10.8 mm Hg; 95% confidence interval (95% CI), 8.6-13.0; range, -5.2 to +28.7 mm Hg; mean diastolic, +8.0 mm Hg; 95% CI, 6.3-9.7; range, -4.4 to +27.1 mm Hg] was detected between days 6 and 10 ($P < 0.0001$ for both) and plateaued thereafter. Variability in blood pressure change did not associate with: age, body size, sex, self-reported race, baseline blood pressure, or steady-state sorafenib plasma concentrations. In the second cohort, the blood pressure elevation was detected during the first 24 hours (mean systolic, +8.2 mm Hg; 95% CI, 5.0-11.3; mean diastolic, +6.5 mm Hg; 95% CI, 4.7-8.3; $P < 0.0001$ for both).

Conclusions: Ambulatory blood pressure monitoring detects the blood pressure response to VEGF signaling pathway inhibition by sorafenib during the first 24 hours of treatment. The magnitude of blood pressure elevation is highly variable and unpredictable but could be important in optimizing the therapeutic index of VEGF signaling pathway inhibitor therapy. (Clin Cancer Res 2009;15(19):6250-7)

Currently, three vascular endothelial growth factor (VEGF) signaling pathway inhibitors, bevacizumab, sorafenib, and sunitinib, are approved for marketing for anticancer indications by the U.S. Food and Drug Administration (1-8). More agents in this class are in late stages of clinical development (9-11). Although the indications for these agents are expanding, little is

known about their therapeutic index or how to dose them and provide supportive care for maximum safety and efficacy.

Hypertension is a mechanism-based toxicity of these agents. Mean systolic and diastolic blood pressure for cohorts of patients receiving VEGF signaling pathway inhibitors increase with exposure to these drugs (12-14) and return to baseline

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Translational Relevance

This study on blood pressure changes in patients who received the vascular endothelial growth factor signaling pathway inhibitor sorafenib has two main applications to the future practice of clinical medicine. First, using this accurate measurement method, it is clear that patients differ in the extent to which their blood vessels respond to this drug, and this could be important to keeping patients safe from side effects and provide new insights about how these drugs work. These insights will allow physicians and scientists to learn how to improve the delivery of these drugs and to develop new, more effective drugs. Second, because this effect can be detected very early in the course of treatment, one day, physicians might be able to determine whether a patient is getting too little or too much drug by measuring the blood pressure and adjust the patient's dose accordingly, and this could possibly lead to better treatment outcomes.

with drug withdrawal (15). These observations suggest that blood pressure might be a pharmacodynamic biomarker of VEGF signaling pathway inhibition that could determine which patients have received a subtherapeutic dose and consequently will not benefit from the treatment, and those who might have received a suprathreshold dose and are at unnecessary risk for systemic toxicities. Mean blood pressure for groups of patients has been reported because, even with standardized office or home measurements, the variability in measurement precludes conventional blood pressure (16) as a pharmacodynamic biomarker for VEGF signaling pathway inhibitors.

Ambulatory blood pressure monitoring is a validated qualified biomarker for antihypertensive drug development with several advantages over and better accuracy than typical office measurements (17). Blood pressure data can be collected over the entire dosing interval. The mean of all measurements collected over 24 hours better correlates with long-term clinical outcomes than a few office measurements. Ambulatory blood pressure monitoring provides reduced measurement variability, so trials require fewer patients and placebos have been shown to have negligible effects on mean ambulatory blood pressure (18).

To assess ambulatory blood pressure monitoring as a pharmacodynamic marker of VEGF signaling pathway inhibition, we prospectively measured ambulatory blood pressure in normotensive advanced-cancer patients to determine the time to development and magnitude of blood pressure elevations caused by sorafenib. Unexpectedly, we found in the initial cohort of 29 patients that most developed blood pressure elevations during the first 10 days of treatment. The measurement schedule was then modified for the second cohort to detect effects of sorafenib on blood pressure during the first day of treatment. In addition, we investigated the relationship between the known interindividual variability in sorafenib steady-state plasma concentrations at the standard dose of 400 mg twice daily and the variability in the blood pressure changes.

Materials and Methods

Patients. Oncologists recruited subjects at the University of Chicago Hospitals outpatient center. The first cohort (29 subjects) began in October 2004, and the second (25 subjects) began accrual in June 2005. Subjects with solid cancers for which appropriate measures had failed or for which there was no known superior treatment, life expectancy \geq 12 wk, age \geq 18 y, and ability to perform at least sedentary work (Eastern Cooperative Oncology Group Performance Status rating of 0 or 1) were eligible. Subjects had to have acceptable organ function by prespecified laboratory measures and provide written informed consent before baseline testing. Patients were excluded if pretreatment blood pressure was $>$ 140/90 mm Hg, if they had history of any arrhythmia other than paroxysmal atrial fibrillation, if they had New York Heart Association Class II or higher congestive heart failure, or if they required more than one antihypertensive agent for any chronic cardiovascular disease management. Patients at risk for acute complications of hypertension were referred to cardiovascular medicine specialists for evaluation; fewer than five enrollees underwent such evaluations, and these prestudy registration data were not collected. Patients with unstable conditions, untreated brain metastases, recent open surgical procedures, seizure disorders, or immune deficiency also were excluded. Treatment previously with VEGF signaling pathway inhibitors (e.g., bevacizumab, sunitinib) or concurrently with other anticancer agents or erythropoiesis-stimulating agents was prohibited. The study protocol was approved by the Institutional Review Board of the Biological Sciences Division of the University of Chicago.

Treatment and safety monitoring with office-based blood pressure measurements. All subjects initially received sorafenib (Bayer) 400 mg orally twice daily, with subsequent dosing adjusted for toxicity, as previously described (5). Subjects underwent clinical evaluations of cancer progression by computed tomographic imaging at least every 8 wk and remained on treatment until sorafenib proved intolerable, clinical presentation was consistent with disease progression, or imaging findings met Response Evaluation Criteria in Solid Tumors for progressive disease (19).

Whether and when to administer antihypertensive therapy was determined by weekly standardized blood pressure measurements collected according to published guidelines (16) with a device (Omron Healthcare) certified by the International Protocol (20). Briefly, these office-based measurement sessions entailed collection of three measurements separated by at least 3 min, with attention to proper positioning of the patient, cuff size, and technique by a trained observer. The mean of three measurements meeting accuracy criteria was used for screening, toxicity grading, and management decisions. Patients with systolic blood pressure \geq 150 mm Hg, diastolic blood pressure \geq 100 mm Hg, or \geq 20 mm Hg more than the baseline measurement had grade 2 hypertension by the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0⁷ and were treated according to structured agent selection and dose titration. If a blood pressure $<$ 140/90 mm Hg was not achieved with two agents maximally titrated over a 3-wk period, the sorafenib was withheld until the goal blood pressure was achieved and restarted at a lower dose. Patients who developed other grade 2 events (commonly including hand-foot skin reaction, diarrhea, and hypophosphatemia) had sorafenib withheld and dose adjusted accordingly.

This study was conducted under Investigational New Drug license 069913 held by the University of Chicago. Bayer, Inc., permitted cross-referencing of their data on file at the U.S. Food and Drug Administration, provided investigational sorafenib tablets, and measured plasma sorafenib concentrations in a blinded fashion.

Ambulatory blood pressure measurement. Ambulatory blood pressure monitoring with an appropriately sized cuff (Oscar PowerPack2,

⁷ http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf

Table 1. Characteristics of 54 evaluable study subjects

Characteristics	n (%)
Sex	
Men	34 (63)
Women	20 (37)
Self-reported race/ethnicity	
White non-Hispanic	46 (85)
Black non-Hispanic	4 (7)
Asian/Pacific Islander	2 (4)
White Hispanic	2 (4)
Age (y)	57 (29-84)
Body mass index (kg/m ²)	26 (15-49)
Pretreatment antihypertensive therapy	
None	39 (72)
β -Adrenergic receptor blocker	8 (15)
Calcium channel blocker	5 (9)
Hydrochlorothiazide	2 (4)
Tumor type	
Renal carcinoma	19 (35)
Sarcoma	13 (24)
Thyroid carcinoma	6 (11)
Esophageal adenocarcinoma	3 (6)
Non-small cell lung cancer	2 (4)
Neuroendocrine carcinoma	2 (4)
Other*	9 (17)

*Includes two patients, each with gastrointestinal stromal tumor and melanoma, and 1 patient with breast cancer, thymic carcinoma, hemangioendothelioma, adenoid cystic carcinoma, and nasopharyngeal carcinoma. Note these percentages add to >100 because of rounding.

SunTech Medical) was done at baseline (1-13 d before commencing treatment), when steady-state plasma concentrations of sorafenib were first reached (between days 6 and 10 posttreatment initiation), and at least once between days 34 and 71 posttreatment initiation. Subjects in the second cohort had an additional 24-h session on the first day,

during administration of the first two doses of sorafenib. Devices were programmed for patients' reported sleep schedules: daytime measurements collected every 10 to 15 min and nighttime every 45 min. For each subject, the unweighted mean of minimum 40 measurements that met device software parameters for quality control collected over 24 h was used as a summary measure for all analyses. The intradevice measurement variability, tested repeatedly on a reference volunteer subject for 24-h sessions throughout the study, was within 2.5 mm Hg systolic and 2 mm Hg diastolic.

Plasma sorafenib concentration measurements. Plasma samples were collected in sodium-heparinized tubes, centrifuged for 15 min immediately after collection at 4°C, and stored at -80°C. Batched samples were shipped on dry ice within 8 mo of collection to Northeast Bioanalytic Laboratories for determination of sorafenib concentration by high performance liquid chromatography/mass spectroscopy with 80% acetonitrile mobile phase (21). For subjects in the first cohort, the minimum measured plasma concentration of total sorafenib was determined from samples that were collected after at least 6 d of continuous sorafenib dosing, ≥ 16 h after the previous dose, and before the next dose (subjects were instructed to hold their morning dose until arrival to the research center and 16 subjects had these samples available). For subjects in the second cohort, the minimum measured total sorafenib plasma concentration from all samples collected on days 8 and 9 was used (25 subjects).

Statistical analysis. Changes in blood pressure were calculated by subtracting baseline values for each subject from each subsequent measurement session. The significance of these changes was determined by paired *t* test and correlated with baseline categorical variables (e.g., sex) by two-sample *t* tests. Pearson *r* was used for determination of the associations among different continuous measurements (e.g., change in blood pressure and age). Correlation between change in blood pressure and plasma sorafenib concentrations also entailed using an ordered logistic regression model wherein change in systolic blood pressure was coded as 0 for <5 mm Hg (no detectable change), 1 for ≥ 5 to 19.9 mm Hg (typical change), and 2 for ≥ 20 mm Hg (high magnitude change), and for change in diastolic blood pressure as 0 for <4 mm Hg, 1 for ≥ 4 to 14.9 mm Hg, and 2 for ≥ 15 mm Hg. Statistical significance was defined as *P* < 0.05. All statistical analyses were done with Stata 10 (StataCorp LP).

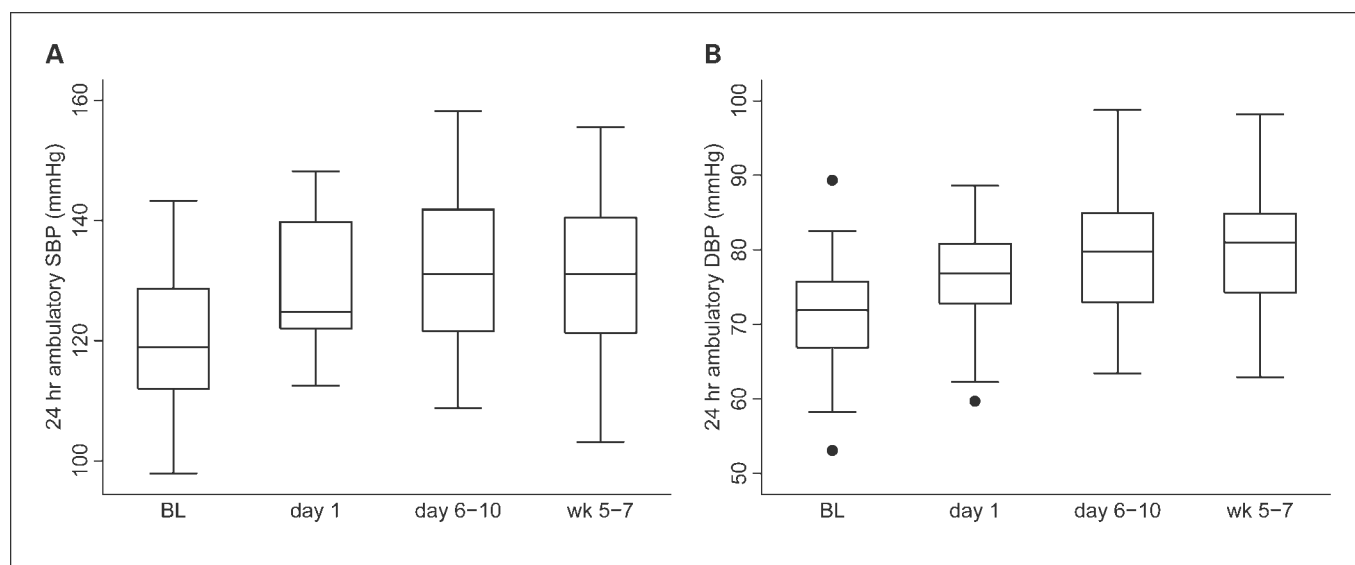


Fig. 1. Time course and distribution of ambulatory blood pressure measurements. Box plots display the population distribution of 24-h mean systolic (A) and diastolic (B) blood pressure measured by ambulatory monitoring. The median for the population is represented by the horizontal line, the interquartile range by the edges of the boxes and values no more than 1.5 \times interquartile range away from the upper or lower quartile by the ends of the bars, with dots as those $>1.5 \times$ interquartile range: before sorafenib administration (BL), over the course of the first 24 h of sorafenib administration (day 1), when steady-state plasma concentrations are first reached (days 6-10), and at a subsequent time point (weeks 5-7) typically 35 to 49 d of sorafenib therapy.

Table 2. Change in ambulatory blood pressure measurements in sorafenib patients

Variable	BL (n = 54)	Day 1 (n = 25)	Days 6-10 (n = 54)	Weeks 5-7 (n = 44)	Change in BP (days 6-10 - BL; n = 54)	Change in BP (day 1 - BL; n = 25)
SBP (mm Hg)						
Mean	120.8	129.1	131.6	131.6	10.8	8.2
SD	10.4	11.3	12.1	11.6	8.1	7.6
Median	118.9	124.8	131.1	131.1	9.4	7.0
Range	97.9 to 143.3	112.5 to 148.2	108.8 to 158.2	103.1 to 155.5	-5.2 to 28.7	-7.2 to 23.9
95% CI					8.6-13.0	5.0-11.3
P					<0.0001	<0.0001
DBP (mm Hg)						
Mean	71.3	76.6	79.2	80.0	8.0	6.5
SD	7.0	7.1	8.1	8.0	6.2	4.5
Median	71.9	76.8	79.8	81	7.3	5.8
Range	53.1 to 89.3	59.7 to 88.6	63.4 to 98.7	62.9 to 98.2	-4.4 to +27.1	-0.7 to 16.7
95% CI					6.3-9.7	4.7-8.3
P					<0.0001	<0.0001

Abbreviations: BL, baseline; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Results

Patient characteristics. Of 70 patients completing baseline evaluation and initiating sorafenib therapy, 54 (77%) had uninterrupted sorafenib dosing and blood pressure measurements collected at baseline and on or after day 6. In this advanced-disease population, 12 patients underwent the initial baseline blood pressure measurement session but were deemed unevaluable because of disease complications interfering with treatment initiation and/or completion of the second blood pressure measurement session. Two subjects failed to adhere to the treatment program and were deemed unevaluable. Two subjects required dose interruptions and did not have steady state plasma sorafenib concentrations at the day 6 to 10 blood pressure measurement session. Characteristics of the 54 evaluable patients are summarized in Table 1.

Quantitative blood pressure response to VEGF signaling pathway inhibition. All subjects were normotensive at baseline by standardized office measurements. When steady-state plasma sorafenib concentrations were first reached during days 6 to 10, the mean change in the 24-hour mean systolic blood pressure was 10.8 mm Hg [95% confidence interval (95% CI), 8.6-13.0; median, 9.4], and for diastolic blood pressure, it was 8.0 mm Hg (6.3-9.7; median, 7.3; $P < 0.0001$ for both). Blood pressure seems to plateau subsequently (Fig. 1 and Table 2). For the 25 subjects undergoing ambulatory blood pressure monitoring on day 1, the mean change in the 24-hour mean systolic blood pressure was 8.2 mm Hg (5.0-11.3; median, 7.0), and for diastolic blood pressure, it was 6.5 mm Hg (4.7-8.3; median, 5.8; $P < 0.0001$ for both; Table 2). Visits after day 10 include fewer patients because of attrition from disease progression or intercurrent serious adverse events. In addition, 14 subjects had active intervention to control the blood pressure elevation safely during the interval between day 10 and the subsequent measurement session (i.e., these patients met National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 grade 2 or 3 hypertension criteria). This medically appropriate intervention was based on the weekly measurements and not the ambulatory measures.

The introduction of antihypertensive therapy in some patients contributes in part to the population plateau effect after steady state concentrations were reached. Given the modest sample of patients, analyses of interindividual variability in blood pressure response and association with various factors focus on the interval between baseline and steady state. During this time the only intervention for all participants was the oral administration of sorafenib at the same dose of 400 mg twice daily.

Interindividual variability in blood pressure response to VEGF signaling pathway inhibition. The magnitude of blood pressure elevation varies among individuals when steady-state plasma sorafenib concentrations are reached (Fig. 2). Eight subjects had an elevation of systolic and diastolic blood pressure nearly twice the mean change (systolic blood pressure ≥ 20 mm Hg

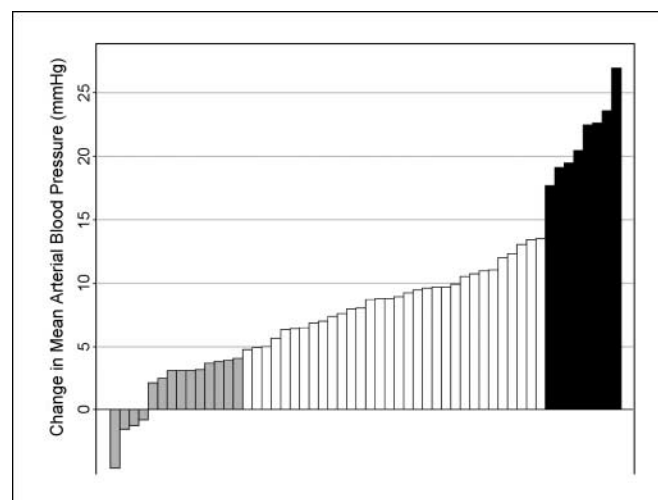


Fig. 2. Change (day 6-10 measurement - baseline measurement) in mean arterial pressure measured by ambulatory monitoring for each patient. The gray bars demarcate 14 subjects with measurements less than twice the limit of detection for change (4.3 mm Hg) in mean arterial blood pressure. The eight subjects identified by dark bars had changes in mean arterial blood pressure more than twice the observed average change (16.7 mm Hg).

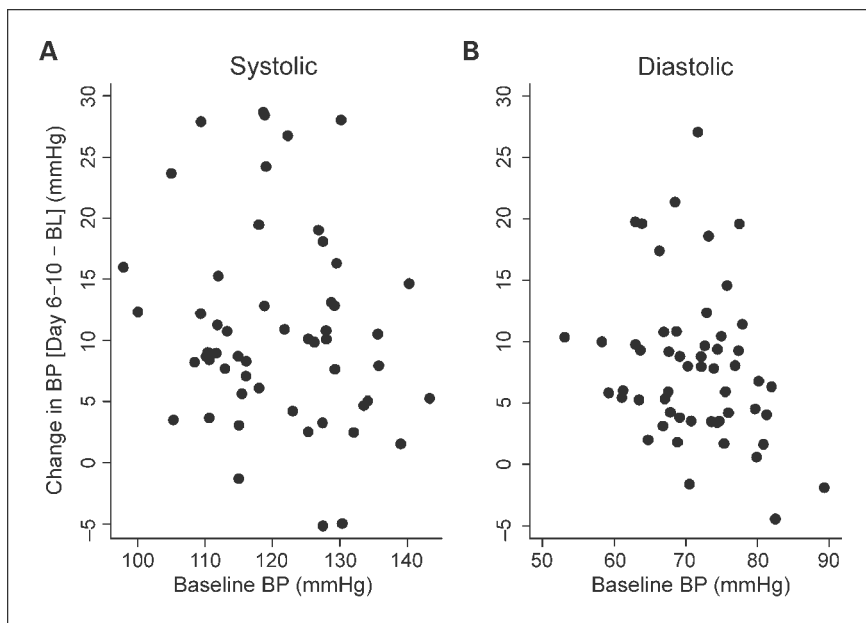


Fig. 3. Correlation between baseline blood pressure and change in blood pressure with exposure to sorafenib. For the 54 patients with complete ambulatory measurements on both sessions at steady state sorafenib dosing, the magnitude of change in blood pressure does not positively correlate with the absolute baseline value for systolic blood pressure ($r = -0.17$; -0.42 to 0.10 ; $P = 0.22$; A) or diastolic blood pressure ($r = -0.27$; 95% CI, $0.50-0.002$; $P = 0.05$; B).

and diastolic blood pressure ≥ 15 mm Hg equating to a mean arterial blood pressure of 16.7 mm Hg) for the study population, whereas 14 subjects had blood pressure elevations less than twice the threshold measurement variability of the devices (for systolic blood pressure ≤ 5 mm Hg and diastolic blood pressure ≤ 4 mm Hg equating to a mean arterial blood pressure of 4.3 mm Hg), essentially no elevation.

There was no significant association of the magnitude of change in systolic or diastolic blood pressure with age, body mass index, sex, self-reported race (white versus other), or tumor type (renal cell versus other). All patients in this study had their baseline blood pressure within the reference range with no more than one antihypertensive agent. Within this pa-

tient population, there was no positive correlation between the magnitude of the baseline blood pressure measurement and the change in blood pressure due to sorafenib exposure for 6 to 10 days (Fig. 3). There also was no association with baseline renal function or presence/absence of antihypertensive therapy.

Association between variability in blood pressure changes and variability in sorafenib pharmacokinetics. As no other readily measurable clinical variables accounted for variability in change in blood pressure during initial sorafenib exposure, we hypothesized that the known pharmacokinetic variability of total plasma sorafenib concentrations (22) might correlate with variability in effects on blood pressure. The relationship is complex (Fig. 4), and to detect any direct correlation between sorafenib plasma

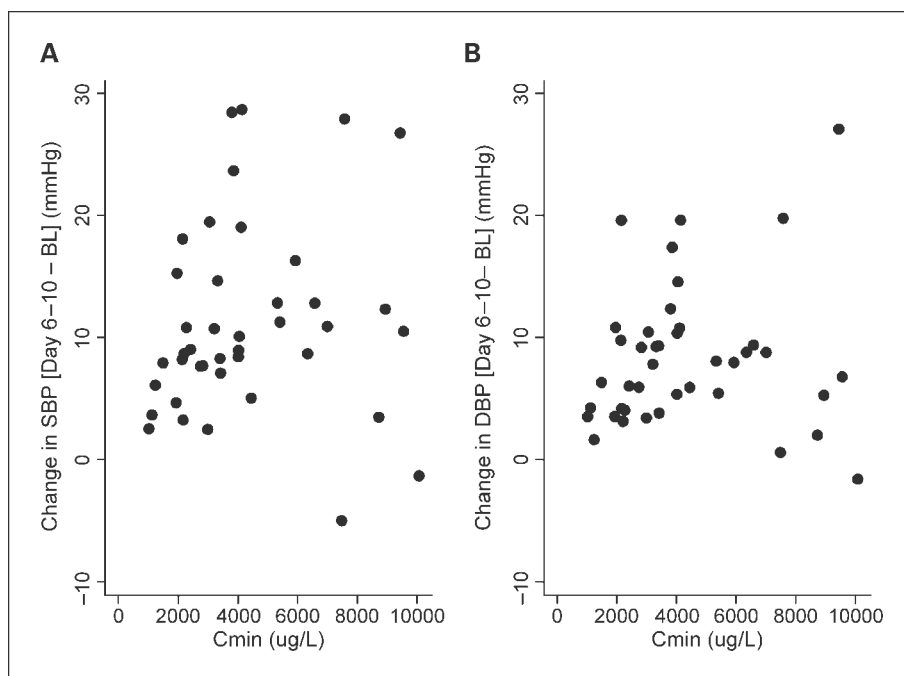


Fig. 4. Absence of correlation between total sorafenib plasma concentrations/exposure and change in blood pressure. The magnitude of change in systolic blood pressure (A) and diastolic blood pressure (B) does not correlate with observed minimum total sorafenib plasma concentrations. For systolic blood pressure, odds ratio is 1.29 (95% CI, $0.63-2.61$; $P = 0.49$), and for diastolic blood pressure, odds ratio is 1.22 (95% CI, $0.62-2.43$; $P = 0.57$).

concentrations and change in blood pressure, an ordered logistic regression model was fit in addition to calculating the Pearson r . For the 41 subjects with minimum observed plasma specimen concentrations available, the change in blood pressure was categorized as no detectable change, typical change, and high-magnitude change (as described in Fig. 2 and Methods). Odds ratios are expressed per 1 SD increase in minimum concentration, that is, per 2,542 ng/ μ L. For systolic blood pressure, odds ratio is 1.29 (95% CI, 0.63-2.61; $P = 0.49$), and for diastolic blood pressure, odds ratio is 1.22 (95% CI, 0.62-2.43; $P = 0.57$). The Pearson r 's were 0.20 ($P = 0.21$) and 0.19 ($P = 0.24$), respectively. These data indicate that there is no direct relationship between the interindividual variability in sorafenib pharmacokinetics and variability in the change in blood pressure due to exposure to sorafenib.

Discussion

In this cohort of advanced cancer patients, we have shown that (a) the time at which sorafenib-induced blood pressure elevation is detectable is as early as the first day of therapy and more readily detected when steady state concentrations of sorafenib are first reached at approximately day 7, (b) the magnitude of this effect varies with several individuals (~25%) having minimal blood pressure change and ~15% of subjects having relatively dramatic elevations over the first week of treatment, and (c) this blood pressure variability is not associated with the baseline blood pressure or the variability in total plasma concentrations of sorafenib with the standard starting dose of 400 mg twice daily.

Blood pressure elevations due to VEGF signaling pathway inhibition were first shown with sorafenib in a cohort of 20 subjects using structured office measurements over the typical clinical evaluation interval of 3 weeks (13). For another VEGF signaling pathway inhibitor, sunitinib, detection at week 1 with home blood pressure monitoring was recently reported (15). Using the more intensive measurement technique of ambulatory monitoring detects changes earlier in the treatment course and more reliably within individual subjects. In this investigation, we did not have the opportunity to compare these two techniques contemporaneously. It will be useful to determine the minimum sampling of blood pressure measurements necessary for accurate assessment of a patient's individual blood pressure response to VEGF signaling pathway inhibitor therapy.

For safe management of normotensive patients receiving these drugs, these data suggest blood pressure measurements should be done no later than when drug steady-state plasma concentrations are first reached. The magnitude of blood pressure elevation even for patients with normal blood pressure is variable and unpredictable. Our findings of a rapid increase in blood pressure with initial exposure to sorafenib are consistent with the hypothesis that VEGF signaling pathway inhibition causes blockade of VEGF-mediated posttranslational activation of endothelial nitric oxide synthase, leading to decreased nitric oxide production and increased vascular tone. As highlighted in studies on VEGF signaling pathway inhibition in a rodent model of pancreatic cancer (23), a second slower mechanism of blood pressure elevation may develop from induction of endothelial cell apoptosis, leading to diminished production of numerous endothelium-derived vasodilatory factors and decreased microcapillary density in at least some organ beds,

causing increased resistance and pressure in larger vessels. Microscopic imaging of the adult mammalian vasculature during treatment with various VEGF signaling pathway inhibitors (24, 25) shows a clear role for VEGF in regulating endothelial cell survival in the nontumor microvasculature. These imaging studies also show that loss of endothelial cell coverage of capillaries is reversible upon cessation of VEGF signaling pathway inhibition. Two subjects in our investigation who had sorafenib withheld or the dose decreased for nonvascular toxicities had decreases in their blood pressure (data not shown), and in a home blood pressure monitoring study, when sunitinib had been withheld for 2 weeks, blood pressure decreased (15). The specific mechanism for this recovery is unclear, but the hypothesis that this represents restoration of microvascular flow and/or endothelial cell repopulation of capillaries is consistent with the time course of these events showed in rodent experiments (25). Scientifically, it would have been ideal to collect ambulatory blood pressure measurements from patients upon failure of treatment to document the time course and magnitude of decline in the blood pressure off sorafenib, but this was deemed an excessive request in this advanced solid tumor patient population. An ongoing trial⁸ examines off-treatment effect early in the course of sorafenib therapy.

Because this effect can be detected so early in the treatment course, it is appealing to think that the magnitude of change in blood pressure could serve as a biomarker for VEGF signaling pathway inhibitors and be used to guide treatment of various malignancies. But to determine how best to use this putative marker to individualize VEGF signaling pathway inhibitor therapy requires answers to three questions:

- 1) Does variability in changes in blood pressure on exposure to VEGF signaling pathway inhibitors reflect pharmacokinetic or pharmacodynamic variability?
- 2) Does the magnitude of blood pressure elevation mark exposure of the individual to differing degrees of VEGF signaling pathway inhibition, differing degrees of endothelial cell apoptosis and endothelial cell reserve, or variability in the capacity of blood pressure regulatory mechanisms to respond to the stress of VEGF signaling pathway inhibition?
- 3) Does the magnitude of pharmacodynamic effects on the systemic vasculature directly reflect the effects on the tumor vasculature and tumor growth, survival, and spread?

Our study addresses the first question, and our findings are consistent with the conclusion that variability in changes in blood pressure due to VEGF signaling pathway inhibition reflects pharmacodynamic variability. The variability in blood pressure response is not associated with the known variability in total sorafenib concentrations in plasma. The blood pressure variability may be better explained by (a) a measure of free concentrations of sorafenib, (b) pharmacokinetic variability of an undetected metabolite of sorafenib (although sorafenib is the predominant molecule in plasma at steady state and is a more potent inhibitor of the VEGF signaling pathway than its detectable metabolites), or (c) physiologic and pharmacodynamic variability, for example, increased sensitivity to eNOS down-regulation or diminished counter-regulatory blood pressure lowering mechanisms.

⁸ <http://clinicaltrials.gov/ct2/show/NCT00436579>

Our study is limited by a number of issues. We had no control group or structured withdrawal of sorafenib to show definitively that the magnitude of blood pressure elevation is directly related to sorafenib exposure and not other factors. A second issue is the flexibility in the scheduling of the blood pressure measurement sessions (some as early as day 6 and others as late as day 11). The timing of the measurement within this interval did not associate with the magnitude of change in blood pressure measured over the interval (data not shown). Because this study was done in a cohort of advanced-solid tumor patients with various malignancies, there is no opportunity to determine fairly the relationship between blood pressure changes and tumor response. Finally, we only measured total sorafenib plasma concentrations, and theoretically unbound concentrations of sorafenib (rather than the total free and protein-bound forms of drug as reported here) might better correlate with change in blood pressure. This investigation determined blood pressure-elevating effects only in patients receiving sorafenib, and although these findings might be true for all VEGF signaling pathway inhibitors, they remain to be confirmed for these other drugs.

As described above, these data suggest two important directions for future research about blood pressure as a mechanism-based effect of VEGF signaling pathway inhibition. As we and others have suggested (14, 26–30), this validated quantitative marker for long-term cardiovascular disease complications is readily applicable to clinical management and could be a useful marker of the effect of VEGF signaling pathway inhibitors on endothelial cell function. Before blood pressure measurement can be applied as a biomarker in cancer therapy, these findings will need to be reproduced in other clinical settings and described for other agents in this class. It will also be important to determine the sources of pharmacodynamic variability and the association of this variability to the antitumor effects of these agents.

In the interim, physicians should be aware that large increases in blood pressure can occur in a short period of time

after treatment initiation. Attentive measurement and management of these unpredictable elevations in blood pressure could avoid acute complications of hypertension that can occur with less frequent surveillance. As recently noted (31), clinicians should recognize that previously collected databases, typically with fields only for hypertension grading scales or intermittently collected nonstandardized office measurements, entail a high degree of variability, making most reports about the relationship between blood pressure and VEGF signaling pathway inhibition inconclusive at this time. To draw conclusions on risk for hypertension among specific patient subsets, effective selection of antihypertensive therapy or hypertension and cancer therapy outcomes would be premature and possibly harmful in the long term (32–36). We advocate careful prospective patient-oriented studies as the most efficient means by which the complexity of these relationships can be unraveled and applied to improve patient care with this important new class of anticancer agents.

Disclosure of Potential Conflicts of Interest

M.L. Maitland has received partial funding from Bayer, Inc. to support biomarker testing in an ongoing, NCI-sponsored clinical investigation of dose escalation of sorafenib. W.M. Stadler has received research funding from Bayer, Inc. for the conduct of clinical investigations and development of imaging biomarkers and has had a consulting agreement with Bayer, Inc. M.J. Ratain has consulted for ONYX. M.L. Maitland and M.J. Ratain are co-inventors on a patent pending filed by the University of Chicago on methods of treating pulmonary arterial hypertension, which includes sorafenib.

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