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Risk Factors for Severe Hypertension and Proteinuria After Treatment With Vascular Endothelial Growth Factor Signaling Pathway Inhibitors Among Patients With Cancer

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INTRODUCTION

Vascular endothelial growth factor signaling pathway inhibitors (VSPIs) treat numerous types of cancers by blocking tumor angiogenesis;[1] however, they are associated with both hypertension and proteinuria. Hypertension has been reported in 20% to 90% of patients.[2,3] The onset of hypertension can vary from hours to weeks, depending upon the half-life of the VSPI.[4] Proposed mechanisms for VSPI-associated hypertension include reduced vasodilatory nitric oxide and prostacyclin, increased peripheral vascular resistance due to increased vasoconstrictive endothelin-1, and development of renal-limited thrombotic microangiopathy. Although it may serve as a marker of antiangiogenic action and treatment efficacy,[S1] severe hypertension can contribute to cardiovascular morbidity and mortality, leading to interruption or discontinuation of VSPIs.[5]

Proteinuria can also occur with VSPI therapy in 21% to 63% of treated patients,[5] and is thought to occur via rarefaction of the peritubular capillary network and disruption of the paracrine signaling between the podocyte and glomerular endothelium. Like VSPI-associated hypertension, proteinuria is associated with cardiovascular disease and poor patient outcomes, necessitating frequent monitoring after starting VSPIs.[6]

Herein, we examine risk factors and time to onset of VSPI-associated ≥grade 3 hypertension and ≥grade 2 proteinuria, the most clinically-relevant forms of proteinuria and hypertension, in adult patients.

with cancer treated with VSPIs between 2016 and 2023 at Massachusetts General Hospital and Dana-Farber Cancer Institute (see Supplementary Table S1 for the International Classification of Disease codes for cancer diagnoses). The methods are described in the Supplementary Methods.

RESULTS

Baseline Characteristics and Incidence

The initial study population included 5236 patients receiving anti–vascular endothelial growth factor (VEGF) angiogenic agents (e.g., bevacizumab), tyrosine kinase inhibitors (TKIs), and multikinase inhibitors (Supplementary Table S2; Supplementary Figure S1).[S2–S4] After exclusions, there were 2485 patients in the hypertension analysis, of whom 590 (23.7%) developed ≥grade

3 hypertension (Supplementary Figure S2A), and 1249 patients in the proteinuria analysis, of whom 507 (40.6%) developed ≥grade 2 proteinuria (Supplementary Figure S2B) in the first year following drug initiation. Among patients with ≥grade 3 hypertension, the median follow-up time was 112 days (interquartile range [IQR], 50–204), while median follow-up time was 125 days (IQR, 61–228) among patients with ≥grade 2 proteinuria.

Patients with ≥grade 3 hypertension were more likely to have a history of hypertension at baseline, lower estimated glomerular filtration rate, and a history of genitourinary cancer (Supplementary Table S3A). Patients with ≥grade 2 proteinuria were more likely to have diabetes, coronary artery disease, congestive heart failure, and lower baseline estimated glomerular filtration rate (Supplementary Table S3B).

The median differences in pretreatment versus posttreatment systolic and diastolic blood pressures for the patients with versus those without high-grade hypertension are shown in Supplementary Figure S3A and B. The incidence of ≥grade 3 hypertension and ≥grade 2 proteinuria was similar among different drug classes (Supplementary Figures S4A and S5A). However, ≥grade 3 hypertension was observed most frequently among patients receiving axitinib (42%) and aflibercept (45%) (Supplementary Figure S4B), and ≥grade 2 proteinuria was most common among patients receiving aflibercept (64%) and sorafenib (61%) (Supplementary Figure S5B).

Time to Onset

≥Grade 3 hypertension occurred at a median of 112 days (IQR, 50–204) following drug initiation (Figure 1a), whereas ≥grade 2 proteinuria occurred at a median of 110 days (IQR, 53–205) (Figure 1b). Median time to onset of proteinuria was shortest among patients receiving TKIs (61 days, IQR 29–176), whereas time to onset of hypertension was shortest among patients receiving multikinase inhibitors (87 days; IQR, 36–231) (Supplementary Figure S6).

Risk Factors

Univariable associations between each variable and the outcomes of interest are shown in Supplementary Table S4, and patterns of missing data for key variables are shown in Supplementary Figure S7. In multivariable-adjusted analyses, age >70 years, a history of genitourinary malignancy, and treatment with direct anti-VEGF angiogenic agents were most strongly associated with ≥grade 3 hypertension (Figure 2a). Other predictors included female sex, baseline hypertension, estimated glomerular filtration rate <90 ml/min/m^2, and serum magnesium <1.8 mg/dl. The strongest risk factors for ≥grade 2 proteinuria were a history of coronary artery disease, baseline systolic blood pressure >160 mm Hg, hemoglobin <11 g/dl, and use of multikinase inhibitors (Figure 2b). Among patients receiving bevacizumab and cabozantinib, there was no association between higher doses of the drug and ≥grade 3 hypertension (Supplementary Figure S8) or with ≥grade 2 proteinuria (Supplementary Figure S9). However, higher doses of pazopanib and sunitinib were associated with both high-grade hypertension and proteinuria.

Treatment Changes and Discontinuation of VSPIs

Among 590 patients with ≥grade 3 hypertension, 261 (44.2%) were treated with an additional antihypertensive, and 44 (7.4%) were switched to a different medication. In both cases, the most common medication that was added, or that a patient switched to, was a calcium channel blocker. Among patients with high-grade proteinuria, 244 of 507 patients (48.1%) patients were treated with an additional agent (most commonly, a calcium channel blocker), and 36 (7.1%) switched medications, most commonly to a diuretic.

Within 30 days and 60 days of the onset of ≥grade 3 hypertension, 137 (23%) and 208 (35%) discontinued VSPIs, respectively (Supplementary Figure S10A and S10B). Within 30 days and 60 days of onset of ≥grade 2 proteinuria, 147 (29%) and 221 (44%) discontinued VSPIs, respectively (Supplementary Figure S10A and S10B).

DISCUSSION

In a cohort of patients with varying cancer types treated with VSPIs, we identified key risk factors for severe hypertension and high-grade proteinuria, important differences in time to onset of each outcome, and relatively high rates of VSPI discontinuation among patients with severe hypertension and proteinuria.

VEGF comprises a family of glycoproteins that bind to 3 receptor tyrosine kinases (VEGF receptor [VEGFR] 1–3) found on numerous tissues, primarily on the surface of vascular and lymphatic endothelial cells.[1] VEGFR2 is abundantly distributed in stromal and malignant vascular tissues[7] as well as in the glomerulus and peritubular capillary endothelium.[6] Inhibition of the VEGFA-VEGFR2 signaling pathway, therefore, has wide-reaching sequelae, including the development of hypertension and proteinuria.

We found a relatively high incidence of ≥grade 3 hypertension and ≥grade 2 proteinuria compared to previous studies, where the incidence of severe hypertension and high-grade proteinuria ranged from 7% to 43% and 1% to 6.7%, respectively.[S5,S6] This variability may be due to different definitions across randomized clinical trials and observational studies.[S6] In addition, whereas previous studies have defined high-

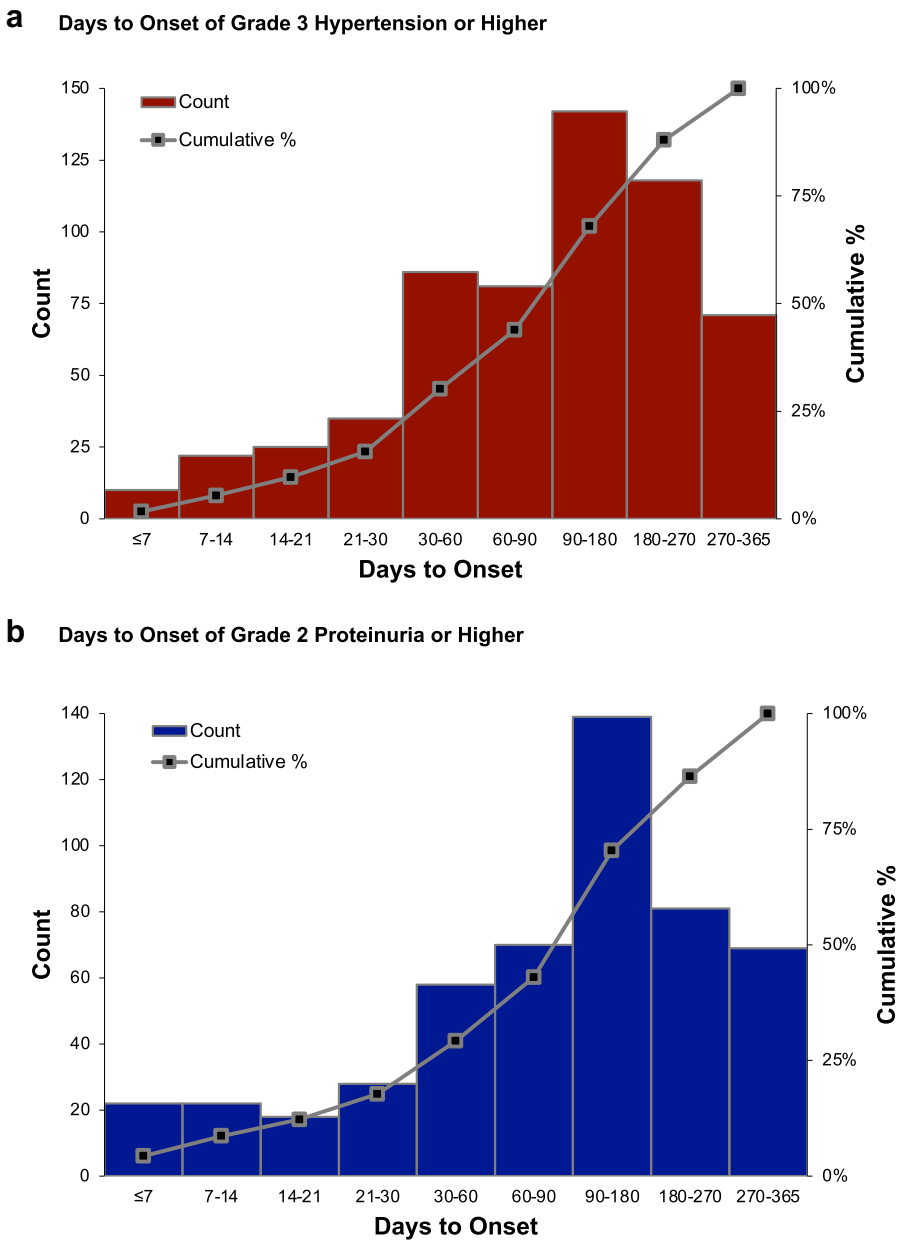

Figure 1. Time to onset of grade 3 hypertension and grade 2 proteinuria or higher. (a) Time to onset of grade 3 hypertension or higher, which was a median of 112 days (interquartile range, 50–204) following the start of drug therapy. (b) Time to onset to grade 2 proteinuria or higher, which occurred at a median of 110 days (interquartile range 53–205).

grade proteinuria as nephrotic range, our definition utilized a lower threshold, but one that is nonetheless associated with inferior clinical outcomes.[S6] We also included patients treated with newer VSPIs such as TKIs and multikinase inhibitors, where the incidence of hypertension and proteinuria may be higher than previously reported.[8]

Previous studies explored risk factors for VSPI-associated hypertension but were limited by small sample size and did not include patients treated with newer VSPIs.[9] Preexisting hypertension and older age have been described as risk factors for VSPI-associated hypertension. However, we identified several additional risk factors such as hypomagnesemia; higher magnesium levels have vasodilatory effects, which may explain these findings.[S7] We also found that antiangiogenic VEGF agents were more strongly associated with severe hypertension compared with TKIs in multivariable-adjusted analyses. The reason for this is unclear, but may be due to the selectivity of certain TKIs, binding affinity, and half-lives of the drugs.

Studies examining risk factors for proteinuria have mostly focused on patients with a specific cancer diagnosis, or those treated with a single agent. One study found that patients with metastatic renal cell carcinoma treated with pazopanib or sunitinib who

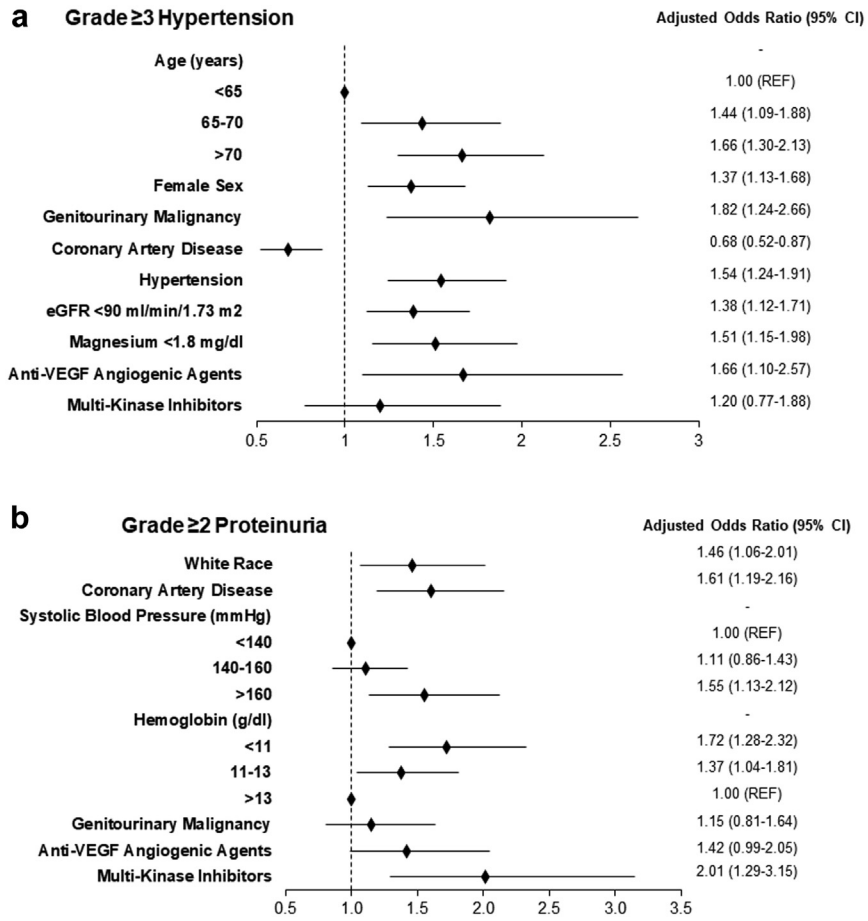

Figure 2. Risk factors for grade 3 hypertension and grade 2 proteinuria or higher. (a) The multivariable-adjusted odds ratios for risk factors for grade 3 hypertension or higher ($n = 2485$), and (b) the multivariable-adjusted odds ratios for risk factors for grade 2 proteinuria or higher ($n = 1249$). Sex was defined based on biologic characteristics. Genitourinary malignancy included bladder, prostate, renal, testicular, and ureter malignancies. For the analysis, genitourinary malignancy was compared to all other cancer types. Tyrosine kinase inhibitors were the reference group (compared to multikinase inhibitors and anti-VEGF angiogenic agents). CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; VEGF, vascular endothelial growth factor.

developed high-grade proteinuria were more likely to have underlying diabetes and higher systolic blood pressure.[S8] Other studies have similarly found that controlling blood pressure is critical in proteinuria prevention.[S9] We observed a class effect, whereby patients receiving multikinase inhibitors were more likely to have proteinuria compared to patients receiving TKIs. These findings are surprising, given the association of TKIs with podocyte injury, which often presents as minimal change disease and focal segmental glomerulosclerosis.[S5]

We found that genitourinary cancer was a risk factor for both high-grade hypertension and proteinuria. The reasons for this are unclear but may be due to the fact that patients with genitourinary cancer often undergo nephrectomy, which has been associated with an increased risk of *de novo* arterial hypertension, as well as proteinuria.[S10–S11] These patients thus warrant closer monitoring for VSPI-associated hypertension and proteinuria.

Management of VSPI-associated hypertension and proteinuria may include dose-reduction of the offending agent, or the addition of other antihypertensives or antiproteinuric agents. Importantly, we found that VSPIs were discontinued in over one-third of patients within 60 days of onset of high-grade hypertension and proteinuria. Although the reasons for discontinuation are not known, these findings are compelling, and suggest that severe hypertension and proteinuria could lead to cessation of potentially life-saving cancer treatments.

Our study is unique in that it included patients with diverse cancer types treated with different VSPIs. Furthermore, we specifically focused on severe hypertension and high-grade proteinuria, which are the most clinically relevant. However, there were limitations. We did not collect data on home blood pressures, medication doses (i.e., dose of antihypertensives or antiproteinuric agents), nor did we ascertain the reason for VSPI cessation. Furthermore, only 74 of the 507 (14.6%) patients with high-grade

proteinuria met the primary outcome based on changes in urine microalbumin-to-creatinine ratio, which reflects common practice at our institutions to monitor proteinuria based on serial urinalyses and urine total protein-to-creatinine ratio instead. Nevertheless, our study has important implications for patients treated with VSPIs, as hypertension and proteinuria can lead to withholding or discontinuation of potentially life-saving therapy, even though these are treatable complications. Modifiable risk factors (e.g., hypomagnesemia, anemia) should be aggressively managed, and patients who are at highest risk should undergo more frequent blood pressure and proteinuria monitoring in order to prevent progression to high-grade hypertension and proteinuria.

DISCLOSURE

PEH is member of the Board of Directors at the American Society of Onconephrology, and the Fellow Editor at ASN KidneyNews; he is also a consultant with Glass Health. KDJ is a cofounder of the American Society of Onconephrology; reports consultancy agreements with Secretome, George Clinicals, PMV pharmaceuticals, and Calliditas. KDJ reports honoraria from the American Society of Nephrology, Lexicomp, and UpToDate.com; and reports serving as Editor-in-Chief of ASN KidneyNews and section editor for onconephrology for Nephrology Dialysis Transplantation. JK serves on the speaker panel for BTG International. MES reports research support from the NIH, NIDDK R01DK140839. She also reports research funding from Gilead, Abbvie, EMD-Serono, Otsuka, Angion, Cabaletta, Novartis, Roche, and Merck outside of the submitted work. She has served on a scientific advisory board for Travere, Novartis, Vera, Calliditas, and Mallinckrodt, and is a Data Monitoring Committee member for Alpine Immune Sciences. SG reports research support from the NIH, NIDDK K23DK125672. She also reports research funding from BTG International, GE Healthcare, and AstraZeneca outside the submitted work. She is a consultant for Secretome, Proletariat Therapeutics, Renibus, and GlaxoSmithKline, and cofounder and President Emeritus of the American Society of Onconephrology.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Research Patient Data Registry at Mass General Brigham and OncDRS from Dana-Farber Cancer Institute, but restrictions apply as they were used under license for the current study, and so are not publicly available. De-identified data are available from Dr. Shruti Gupta upon reasonable request via email and after execution of a data use agreement with Mass General Brigham.

SUPPLEMENTARY MATERIAL

Supplementary File (WORD)

Supplementary Methods.

Supplemental References.

Figure S1. Classification of VSPIs based on targets.

Figure S2. Flowchart of inclusion for hypertension and proteinuria analyses.

Figure S3. Differences in pretreatment versus posttreatment systolic and diastolic blood pressures.

Figure S4. Incidence of ≥grade 3 hypertension by drug type and medication.

Figure S5. Incidence of ≥grade 2 proteinuria by drug type and medication.

Figure S6. Time to onset of ≥grade 3 hypertension and ≥grade 2 proteinuria, by medication type.

Figure S7. Patterns of missing data.

Figure S8. Incidence of ≥grade 3 hypertension by medication dose.

Figure S9. Incidence of ≥grade 2 proteinuria by medication dose.

Figure S10. Discontinuation rates among VSPI recipients at 30 and 60 days.

Table S1. International Classification of Disease codes for cancer diagnoses.

Table S2. List of vascular endothelial growth factor signaling pathway inhibitors (VSPIs).

Table S3. Baseline characteristics of patients with and without ≥grade 3 hypertension and ≥grade 2 proteinuria.

Table S4. Unadjusted analyses for ≥grade 3 hypertension and ≥grade 2 proteinuria.

STROBE Statement.

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