Kidney Case Conference: How I Treat

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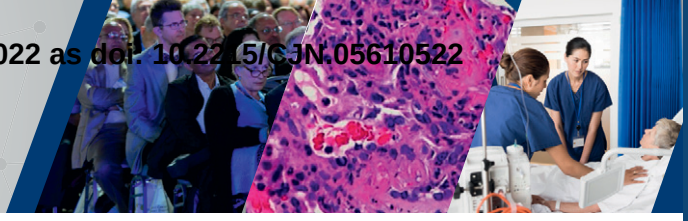

How I Manage Hypertension and Proteinuria Associated with VEGF Inhibitor

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Introduction

Antiangiogenesis agents are frequently used anticancer agents in oncology practice. Proteinuria and hypertension are side effects commonly seen with the use of this class of drugs. The incidence of high-grade (grade 3 or 4) proteinuria with bevacizumab is 2% and the incidence of hypertension is 8%–25% in patients treated with bevacizumab (1). Here, we will discuss the practical approach to manage proteinuria and hypertension, the two common side effects of vascular endothelial growth factor (VEGF) inhibitors.

Case

A 64-year-old woman with a history of well-controlled hypertension (on 5 mg of amlodipine) and ovarian cancer is referred for evaluation of worsening hypertension and new-onset proteinuria. She was recently started on intravenous bevacizumab after failing standard platinum-based therapy. After the first cycle, she noted worsening hypertension, with average readings in the 170/100 range. At this time, her amlodipine dose was increased to 10 mg/d. Later, she presented with increased lower-extremity edema and unchanged BP readings. On examination, her BP was 170/100 mm Hg. She had 1+ bilateral lower extremity edema. Her laboratory data revealed normal kidney function (creatinine =1 mg/dl). A spot urine protein-creatinine ratio was elevated at 2.8.

How to Monitor the Patient?

Proteinuria should be quantified before initiating therapy. Patients treated with VEGF inhibitors should be monitored for proteinuria by checking spot urine protein/creatinine. There are no data on how to start therapy if the patient already has proteinuria. If there is >2 g proteinuria, the cause must be defined by kidney histology if possible and treated with medications before introducing VEGF inhibitor. If there is <2 g proteinuria, treatment with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) preceding the introduction of VEGF inhibitor by 1–2 weeks would be desirable. BP should also be evaluated prior to treatment initiation. Once treatment starts, we recommend weekly BP measurements during the first cycle of therapy as high readings are most likely to occur during this time (2); thereafter, patients should be encouraged to keep a home BP log for noticeable trends.

How to Treat?

There are some data suggesting that proteinuria correlates with overall response but not survival rate. Overall, it seems that both hypertension and proteinuria are associated with the duration of bevacizumab treatment and do not represent an independent prognostic factor (3). Treatment can be continued in most cases involving non–nephrotic-range proteinuria and hypertension. Usually, proteinuria can be aggressively managed with an ACEI or an ARB (Figure 1).

Data on the development of hypertension and its association with improved survival from a cancer standpoint remain conflicting, with only some studies indicating improved overall survival (4,5).

If during routine follow-up, BP is noted to be >140/90 mm Hg, treatment should be initiated. First-line drugs usually include an ACEI or an ARB, which offers the additive benefit in reducing the proteinuria that is commonly seen with VEGF inhibitors. In the absence of proteinuria, dihydropyridine calcium channel blockers (*e.g.*, amlodipine and nifedipine), which lead to smooth muscle relaxation and are potent vasodilators, could also be used.

Use of nondihydropyridine calcium channel blockers concomitantly with tyrosine kinase inhibitor should be avoided as they suppress the cytochrome P450 pathway; this leads to the inhibition of the tyrosine kinase inhibitor metabolism, leading to increased levels with worsening hypertension. Second-line drugs include β-blockers. Nonselective β-blockers, such as nebivolol and carvedilol, have antiangiogenic effect and may offer additional antitumor benefit (6).

Although diuretics can also be used, caution is advised as patients with cancer usually suffer from decreased appetite, nausea, vomiting, and diarrhea due to chemotherapy and remain at high risk of developing volume depletion and prerenal AKI.

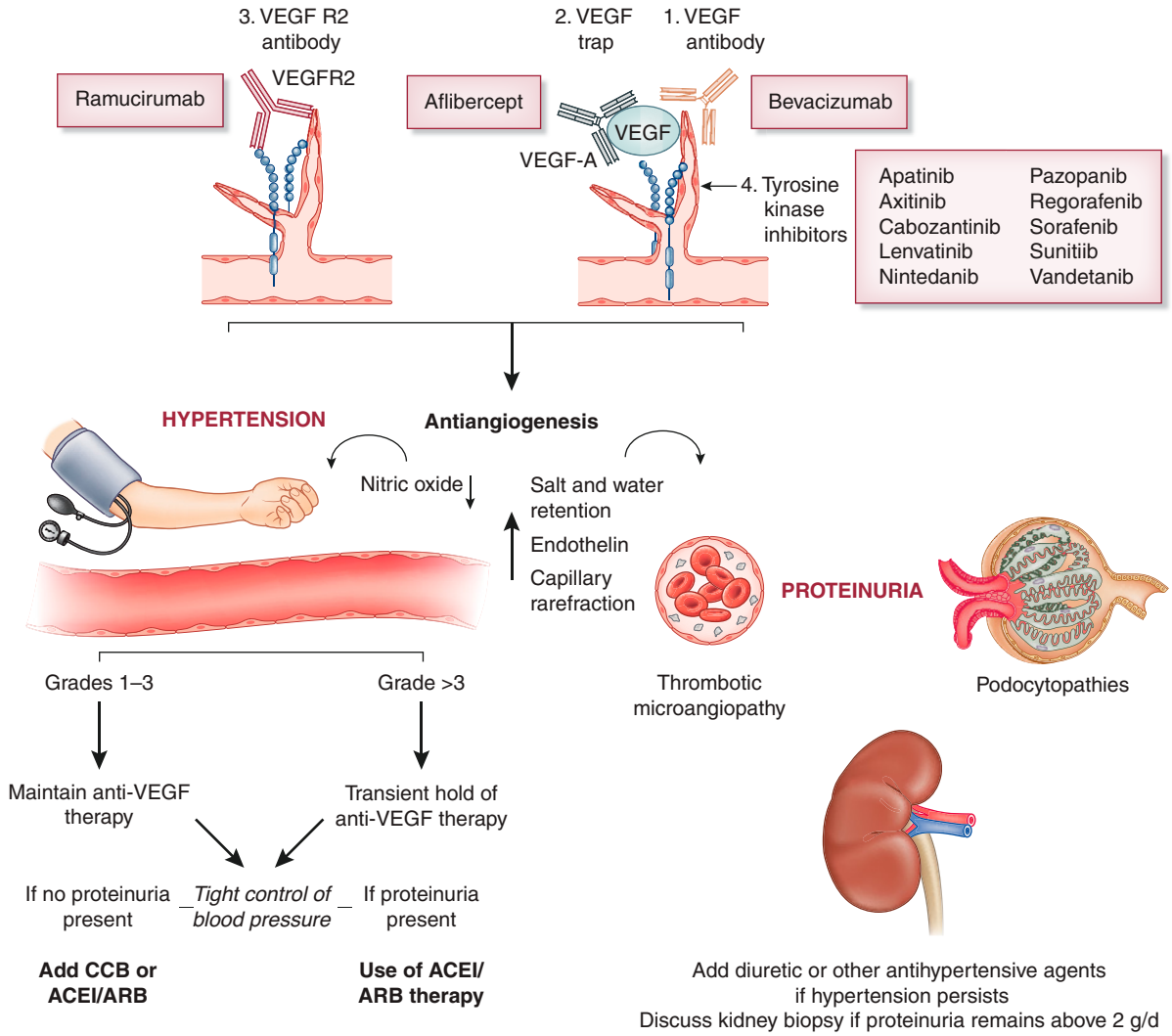

Figure 1. | **Adverse effects of antiangiogenic therapy on glomerular cells and vessels.** Vascular endothelial growth factor (VEGF) inhibitors can work at different sites: (*1*) humanized mAb directed against VEGF (*e.g.*, bevacizumab), (*2*) soluble "decoy" receptors that bind to VEGF (VEGF trap; *e.g.*, aflibercept), (*3*) antibodies targeting the VEGF receptor (*e.g.*, ramucirumab), and (*4*) small molecule tyrosine kinase inhibitors acting on the VEGF receptors (*e.g.*, sunitinib). Multiple pathophysiologic mechanisms are suggested for the development of hypertension with VEGF inhibitors: inhibition of VEGF leading to suppression of nitric oxide synthase and reduction in nitric oxide production, which lead to vasoconstriction; increase in endothelin levels leading to vasoconstriction; reduction in sodium excretion with a right shift in the pressure natriuresis curve resulting in volume expansion; and microvascular rarefaction. Development of kidney-limited thrombotic microangiopathy (TMA) also manifests as new onset of worsening hypertension. VEGF inhibitors can cause TMA, whereas VEGF tyrosine kinase inhibitors can cause podocytopathies of various types, such as minimal change disease, FSGS, and collapsing glomerulopathy. Grades 1–3 hypertension (HTN) can be managed by antihypertensive medications along with continuation of VEGF inhibitors. Development of grade 3 HTN calls for transient discontinuation and a decrease in the dose of the VEGF inhibitors along with up-titration of BP medications. Development of posterior reversible encephalopathy syndrome, TMA, malignant hypertension, and nephrotic-range proteinuria warrants discontinuation of treatment. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) can be used as the first line for the management of HTN with proteinuria, whereas calcium channel blockers (CCBs) or ACEIs/ARBs can be used as the first line for the management of HTN without proteinuria. VEGF-A, vascular endothelial growth factor A; VEGFR2, vascular endothelial growth factor receptor 2.

Should We Do a Kidney Biopsy?

Proteinuria after inhibition of VEGF signaling will frequently disappear upon stopping the responsible agent and achieving BP control. Biopsy is rarely done in these patients for different reasons, such as history of nephrectomy, difficult-to-control hypertension, thrombocytopenia, and assumption that the biopsy will not change the plan.

In our opinion, because treatment options and prognosis might be influenced by kidney histologic findings, a kidney biopsy should be pursued whenever feasible.

In the cases of proteinuria >2 g/d, hematuria, or biochemical evidence of impaired kidney function, we recommend kidney biopsy for the following reasons. (*1*) More than 50% of cases of thrombotic microangiopathy (TMA)

secondary to VEGF inhibitors are localized to the kidney (7). (2) Proteinuria induced by anti-VEGF therapy, even if it is low grade and without associated kidney insufficiency, may reflect a serious histologic kidney disease (8). (3) Proteinuria may be related to a paraneoplastic membranous nephropathy requiring therapeutic strengthening rather than stopping the anti-VEGF.

Stop or Not to Stop?

In clinical practice, the decision to continue, discontinue, or change a treatment remains challenging. Careful risk-benefit assessment for individual patients is important and should take into account risk factors related to the host and the tumor. The decision to stop VEGF inhibitors or to switch to alternative agents should be made in close collaboration between an onconephrologist and an oncologist in a multidisciplinary setting. Generally, development of posterior reversible encephalopathy syndrome, hypertensive emergency, nephrotic-range proteinuria, and TMA are considered reasons to discontinue the offending agent (9,10).

"When to stop" may be interpreted in two ways: either the temporary suspension of VEGF inhibitors without any loss of benefit or a final decision to stop. In many cases, this decision depends on the interpretation of the outcome change from baseline. When the change in outcome indicates effectiveness, continuing the treatment is a logical decision. Similarly, discontinuing the treatment is appropriate when it has not been effective. Often, the problem arises when we have to consider stopping an effective treatment due to its detrimental effects on the kidney.

If the oncologist has a therapeutic alternative as effective as VEGF inhibitor, treatment must be "definitively" stopped. If the VEGF inhibitor treatment remains the "only effective" treatment in this case, it must be reintroduced, preferably after a few weeks of ACEI/ARA2 treatment and at half the dose at the start; then, it can be adapted according to clinical efficacy and tolerance. In general, treatment reintroduction or continuation must meet two requirements: a rigorous and necessary monitoring of BP, kidney function, and hematologic parameters and the discontinuation of treatment in the case of recurrence of TMA.

Probably, some patients can be maintained on antiangiogenic therapies despite the development of hypertension and proteinuria. Tight control of BP may allow patients to continue antiangiogenic therapy. However, the long-term kidney consequences of antiangiogenic therapy in patients who do develop hypertension and/or proteinuria remain unknown.

Studies are necessary to evaluate the effectiveness of eculizumab during TMA induced by an anti-VEGF if the anti-VEGF cannot be stopped, like its effectiveness in TMAs induced by mitomycin C or gemcitabine. With growth of onconephrology as a subspecialty, we should be able to provide comprehensive care for these complex patients.

Disclosures

A. Rashidi reports being a founding member of the American Society of Onconephrology (ASON) and serving as the treasurer of ASON and serving on the speakers bureau for Bayer Pharmaceutical Company and OTSUKA Pharmaceutical Company. R. Wanchoo reports employment with Northwell Health, serving as an associate editor of *Journal of Onconephrology*, serving on the editorial board of *Clinical Kidney Journal*, and being a founding member of ASON. The remaining author has nothing to disclose.

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Author Contributions

A. Rashidi wrote the original draft, and H. Izzedine, A. Rashidi, and R. Wanchoo reviewed and edited the manuscript.

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