Oncohypertension: A New Field in the Making

By Prakash Gudsoorkar

In oncology, survivorship focuses on the health and well-being of a person with cancer from the time of diagnosis until the end of life (1). Hypertension is a growing global public health problem and a contributor to cardiovascular disease (CVD) (2). The relationship among hypertension, cancer, chronic kidney disease (CKD), and CVD is multifaceted, sharing common risk factors, such as smoking, obesity, and metabolic syndrome. For the same reasons, oncohypertension is an emerging subspecialty focusing on the close interplay between hypertension and cancer (3, 4). Hypertension in patients with cancer can be broadly categorized into worsening of preexisting hypertension, paraneoplastic syndrome (i.e., from cancer itself), and hypertension from chemotherapeutic agents and from adjuvant therapies used to treat cancer (Figure 1).

Paraneoplastic hypertension

The prototype example of paraneoplastic hypertension in association with renal cell cancer occurs in 14% to 35% of the cases (5). Pathogenic mechanisms implicated are upregulation of the renin angiotensin aldosterone system (RAAS), ectopic production of erythropoietin, and secretion of vasoactive peptides, such as endothelin 1 and adrenomedullin.

Antihypertensive medications and cancer risk

Over the past few decades, several studies have examined the association between distinct classes of antihypertensive agents and cancer risk. However, each of these observational studies has important caveats and confounders, leaving conflicting results and uncertainty. Even if antihypertensives are associated with a small increased risk of cancer (e.g., thiazides and calcium channel blockers: skin cancer; angiotensin receptor blockers: lung cancer), they likely do not outweigh the known cardiovascular and mortality benefits (6).

Hypertension from cancer therapy

To prevent acute and long-term cardiovascular effects, optimal and timely management of hypertension in survivors of cancer cannot be overstated. Antihypertensive therapies need to be tailored to underlying comorbidities, such as diabetes, heart failure, and others. Hypertension is one of the most common vascular toxicities (class effect) seen in 25%–30% of patients treated with vascular endothelial growth factor inhibition (VEGFi; e.g., bevacizumab, sorafenib, and sunitinib) (7). It is mediated by vasoconstriction (decreased production of endothelial nitric oxide synthase [eNOS]), decreased vascular compliance, and kidney injury (e.g., thrombotic microangiopathy phenotype) (Figure 2).

Polymorphisms in the VEGF gene predispose certain patients to the vasculotoxic effect of VEGFi, for example, single nucleotide polymorphisms in Egl nine homolog 3, epidermal growth factor, WNK lysine-deficient protein kinase 1, and the kinase insert domain receptor gene (8). The current data obtained from clinical trials and physiological studies suggest that dihydropyridine calcium channel blockers (avoid diltiazem or verapamil and inhibit cytochrome P450 3A4 leading to higher levels of drugs, such as sunitinib and sorafenib) and RAAS blockers can be considered as first-line antihypertensive therapies for hypertension mediated by VEGFi (Figure 3) (9). RAAS blockers directly cause vascular smooth muscle relaxation and upregulate NO production leading to microcirculatory changes and decreased blood pressure. In addition, angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) help reduce proteinuria that commonly occurs with VEGFi.

Radiation exposure and hypertension

Radiation therapy that involves the head or neck can lead to baroreflex failure and to associated difficult-to-treat labile hypertension and hypertensive crisis (10). Radiation nephropathy occurs in approximately 20% of irradiated subjects and can have various clinical presentations, such as acute radiation nephritis, chronic radiation nephropathy (chronic thrombotic microangiopathy), malignant hypertension, and benign hypertension.

Oncohypertension is an emerging subspecialty in the field of onconephrology and cardio-oncology, as hypertension lies at the intersection of both specialties. Hence, a multidisciplinary team—consisting of oncologist, nephrologist, cardiologist, pharmacist, and primary care physician—should form the framework of an oncohypertension clinic. ■

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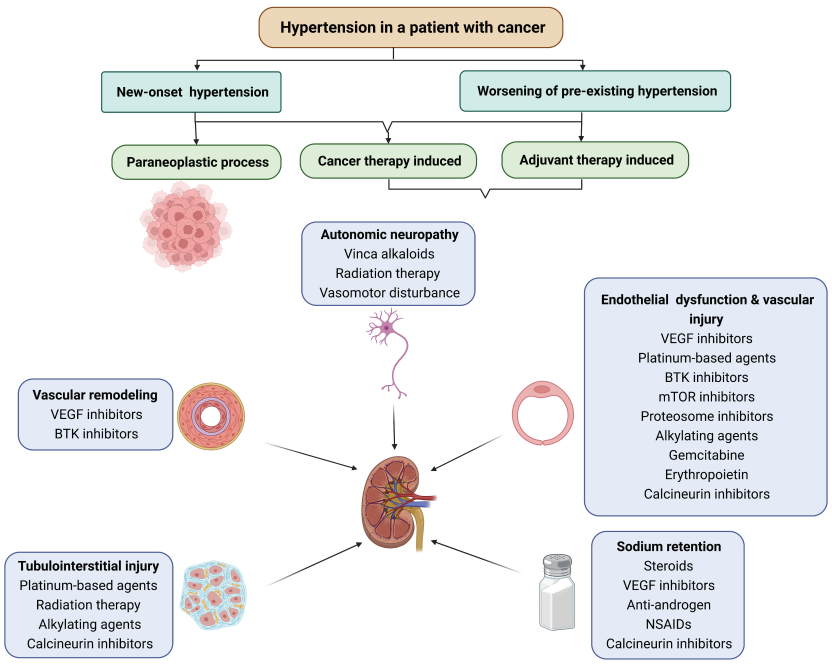
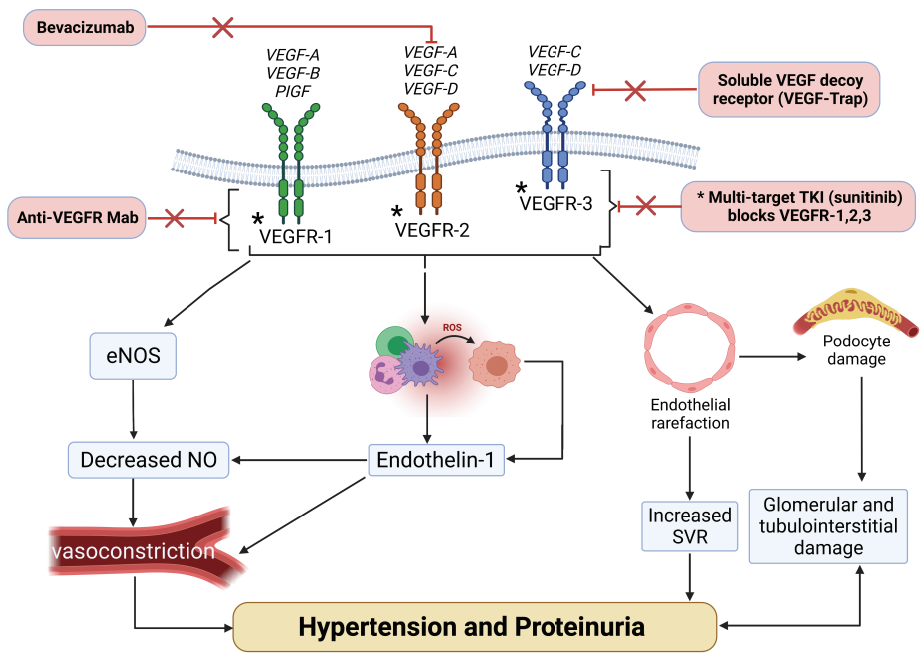
The author reports no conflicts of interest.

Figure 1. Hypertension in a patient with cancer



BTK, Bruton tyrosine kinase; mTOR, mechanistic target of rapamycin; NSAIDs, non-steroidal anti-inflammatory drugs. Figure created using Biorender.com.

Figure 2. Pathophysiology of development of hypertension and proteinuria from VEGFi

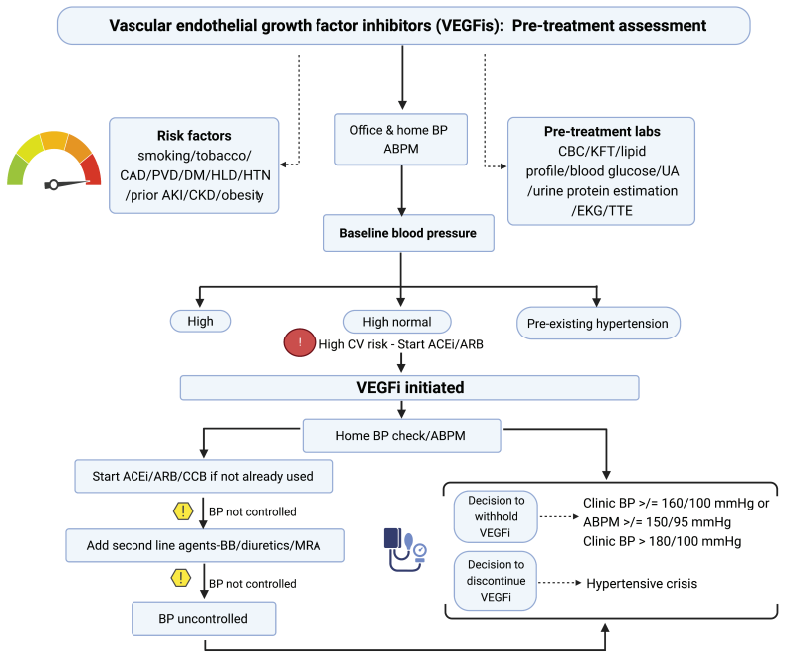


Mab, monoclonal antibody; PIGF, placental growth factor; ROS, reactive oxygen species; SVR, systemic vascular resistance; TKI, tyrosine kinase inhibitor; VEGFR, VEGF receptor. Figure created using Biorender.com.

References

1. Denlinger CS, et al. Survivorship: Introduction and definition. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2014; 12:34–45. doi: 10.6004/jnccn.2014.0005
2. Arima H, et al. Mortality patterns in hypertension. *J Hypertens* 2011; 29 (Suppl 1):S3–S7. doi: 10.1097/01.hjh.0000410246.59221.b1
3. Gudsoorkar P, et al. Onco-hypertension: An emerging specialty. *Adv Chronic Kidney Dis* 2021; 28:477–489.e1. doi: 10.1053/j.ackd.2021.09.011
4. Ruf R, et al. Onco-hypertension: Overview of hy-

Figure 3. Approach to management of hypertension from VEGFi



ABPM, ambulatory blood pressure monitoring; AKI, acute kidney injury; BB, beta blocker; BP, blood pressure; CAD, coronary artery disease; CBC, complete blood count; CCB, calcium channel blocker; CV, cardiovascular; DM, diabetes mellitus; EKG, electrocardiogram; HLD, hyperlipidemia; HTN, hypertension; KFT, kidney function test; MRA, mineralocorticoid receptor antagonist; PVD, peripheral vascular disease; TTE, transthoracic echocardiography; UA, urine analysis. Figure created using Biorender.com.

pertension with anti-cancer agents. *JON* 2021; 5:57–69. doi: 10.1177/23993693211001374
5. Sufrin G, et al. Hormones in renal cancer. *J Urol* 1977; 117:433–438. doi: 10.1016/s0022-5347(17)58490-6
6. Gandini S, et al. Anti-hypertensive drugs and skin cancer risk: A review of the literature and meta-analysis. *Crit Rev Oncol Hematol* 2018; 122:1–9. doi: 10.1016/j.critrevonc.2017.12.003
7. Abdel-Qadir H, et al. Cardiovascular toxicity of angiogenesis inhibitors in treatment of malignancy: A systematic review and meta-analysis. *Cancer Treat Rev* 2017; 53:120–127. doi: 10.1016/j.ctrv.2016.12.002
8. Lambrechts D, et al. Genetic markers of bevacizumab-induced hypertension. *Angiogenesis* 2014; 17:685–694. doi: 10.1007/s10456-014-9424-7
9. Caletti S, et al. Management of VEGF-targeted therapy-induced hypertension. *Curr Hypertens Rep* 2018; 20:68. doi: 10.1007/s11906-018-0871-1
10. Ketch T, et al. Four faces of baroreflex failure: Hypertensive crisis, volatile hypertension, orthostatic tachycardia, and malignant vagotonia. *Circulation* 2002; 105:2518–2523. doi: 10.1161/01.cir.0000017186.52382.f4

Perspective on Onconephrology from a Cancer Doctor

By Oscar B. Lahoud

In the past decades, the field of hematology-oncology has greatly evolved, bringing to practice the routine use of novel therapies with various mechanisms of action, including chemotherapeutic, immunotherapeutic, and targeted agents, which are often combined into complex regimens (Figure 1).

With these ongoing advances, unique drug-drug interactions, treatment timing, dosing challenges, as well as toxicity profiles have emerged, requiring more advanced expertise from our subspecialty consultants who co-manage these patients. My practice focuses on patients with hematologic malignancies, with a particular interest in plasma cell dyscrasias. These encompass a large spectrum of diseases with unique presentations, a wide range of potential organ involvement, as well as multiple distinct treatment options that combine traditional chemotherapeutic agents with the most novel cellular therapies. Impaired kidney function in a patient with plasma cell dyscrasia could be attributable to any of the following:

- worsening of the disease, leading to monoclonal immunoglobulin deposition in the renal tubules
- amyloid fibrils depositing in the glomeruli, causing nephrotic syndrome
- thrombotic microangiopathy from a calcineurin inhibitor after an allogeneic hematopoietic stem cell transplant
- syndrome of inappropriate anti-diuresis related to the use of an alkylator (cyclophosphamide or melphalan)
- acute interstitial nephritis caused by treatment (e.g., lenalidomide) or other supportive drugs (e.g., anti-microbials and contraindicated non-steroidal anti-inflammatory drug analgesics)
- autoimmune nephritis for a patient in an immunotherapy trial
- complex nephrotoxicity from other chemotherapy (e.g., cisplatin)

The intricacies in determining the cause of kidney dysfunction and optimal course of management demand true experts in the field.

To better serve our most challenging patients, at our institution, we have established monthly, multi-disciplinary amyloidosis tumor boards that include subspecialized hematologists, pathologists, oncocardiologists, and onconephrologists who partake as an integral part of our collective discussion and treatment of patients. On a personal basis, having reliable, devoted onconephrologists working with our group affords us the essential reassurance so that we can focus medical decision-making on the very best personalized therapeutic intervention for our patients, knowing our colleagues will be there to prevent and/or address any potential kidney complication that might arise. Oncologists and general nephrologists alike have come to depend on the expertise of onconephrologists for the elaborate evaluation and management of cancer patients with kidney diseases. Onconephrologists have naturally become an indispensable part of cancer care. As the scope of practice for medical academicians has narrowed down to one's exclusive area of research and clinical proficiency, academic onconephrologists have emerged to lead and work together with other oncologic subspecialists to collaboratively advance the field and enhance the care of the patients we serve. ■

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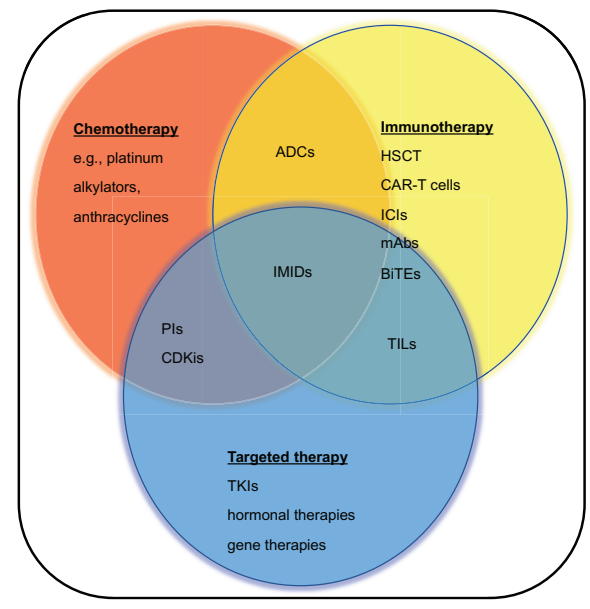
Figure 1. Examples of cancer-directed therapies



Therapies include chemotherapy, immunotherapy, and targeted therapies, as well as examples of hybrid agents. ADCs, antibody-drug conjugates; BiTEs, bispecific T-cell engagers; CAR-T cells, chimeric antigen receptor T-cells; CDKis, cyclin-dependent kinase inhibitors; HSCT, hematopoietic stem-cell transplantation; ICIs, immune checkpoint inhibitors; IMIDs, immunomodulating drugs; mAbs, monoclonal antibodies; PIs, proteasome inhibitors; TILs, tumor-infiltrating lymphocytes; TKIs, tyrosine kinase inhibitors.