

Review

Collateral Renal Injury: Is Nephrotoxicity the Inevitable Cost of Anti-VEGF and ICI Synergy?

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Abstract

Antiangiogenic therapies and immune checkpoint inhibitors (ICIs) have improved cancer outcomes but may cause kidney adverse events.

This mini-review summarizes the mechanisms, clinical manifestations, and management of nephrotoxicity associated with anti-vascular endothelial growth factor (VEGF) agents, VEGFR-targeted multikinase inhibitors, and ICIs.

The mechanisms of kidney injury differed according to the therapeutic class. VEGF pathway inhibition disrupts glomerular barrier integrity, leading mainly to hypertension, proteinuria, kidney dysfunction, and thrombotic microangiopathy. Multikinase inhibitors may also cause electrolyte abnormalities. ICIs most commonly induce acute interstitial nephritis, although glomerular diseases, including pauci-immune glomerulonephritis, podocytopathies, and C3 glomerulonephritis, have also been reported. Combined anti-VEGF and ICI treatment may further increase the risk of proteinuria. Management depends on the type and severity of kidney injury and may require treatment interruption, kidney biopsy, glucocorticoids, or other immunosuppressive therapies.

Early recognition and multidisciplinary management may mitigate nephrotoxicity while preserving optimal oncological treatment.

Keywords: angiogenesis inhibitors, anti-VEGF therapies, Immune checkpoint inhibitors, acute kidney injury

Introduction

Significant progress in the field of cancer therapy has been made in the last several years by using angiogenesis inhibitors, anti-VEGF therapies, both as monotherapy and in combination with other anticancer therapies such as Immune checkpoint inhibitors (ICIs). Although these agents have revolutionized the treat-

ment of cancer and are now the backbone of therapy for several malignancies, their use is associated with possible kidney consequences such as proteinuria and acute kidney injury (AKI). Given that patients with preexisting cardiovascular disease and kidney impairment are often excluded from clinical trials of cancer therapies and that the patients who are enrolled in trials are usually in better overall health condition, the incidence of adverse events is likely to be underestimated in clinical practice.

In this mini review, we discuss the relationship between kidney function and specific antineoplastic agents, with a focus on their toxic effects.

Molecularly targeted therapies

Vascular Endothelial Growth Factor (VEGF) is the key driver of tumour-related angiogenesis and acts through interaction with VEGF receptors (VEGFRs) expressed on tumour endothelial cells. Importantly, VEGF is also expressed on glomerular podocytes, distal tubules, and collecting ducts. The VEGF pathway plays a role in the substantial cross talk that exists between podocytes and endothelial cells that enables appropriate glomerular filtration and perfusion. Podocytes release VEGF, which can then bind VEGFR-2 on the glomerular endothelial cells. VEGF is involved in the proliferation, differentiation, and survival of mesangial and endothelial cells, and has a pivotal role in maintaining the structure and function of the glomerular barrier. In its absence, podocytes and endothelial cells are unable to mature and proliferate, which prevents the formation of capillaries and veins. The reduced production of VEGF by podocytes induces the loss of glomerular and mesangial cells [1-3]. Notably, the pleiotropic effect of VEGF on kidneys accounts for all the different histological effects of anti-VEGF agents (endotheliosis, glomerulosclerosis, hyalinosis, different types of glomerulonephritis, and thrombotic microangiopathies [2]).

Common kidney side effects of **anti-VEGF drugs** include proteinuria, hypertension, kidney dysfunction, thrombotic microangiopathy, and in some cases, kidney failure [2,3]. The development of proteinuria induced by anti-VEGF agents is thought to be driven by a combination of glomerular endothelial cell damage, podocyte dysfunction, and hemodynamic alterations. More specifically, loss of the normal control of VEGF-A expression, leads to structural and functional changes in glomerular cells. In addition, antagonism of VEGF dysregulates kidney-repair processes in the early stages of renal damage, thus increasing the risk of glomerulosclerosis. In addition, the inhibition of VEGF leads eventually to a loss of selective glomerular permeability. Proteinuria might also be caused by increased intraglomerular pressure secondary to arterial hypertension [1]. The binding of VEGF to its receptors increases vascular permeability, induces cell division and differentiation, and blocks apoptosis and cellular ageing. Consequently, VEGF inhibition reduces the ability of cell renewal, increases apoptosis in vascular endothelial cells, promotes rarefaction of capillaries and arterioles, and interferes with the cellular production of vasodilators, such as nitric oxide and prostacyclin, favoring vasoconstriction, increased peripheral resistance and decreased renal excretion of sodium [1]. The main driver of VEGF inhibitor induced hypertension and kidney toxicities seems to be an upregulation in endothelin (ET)-1 via the stimulation of the ETA receptor. This in turn, contributes to the increases in reactive oxygen species (ROS) and a reduction in nitric oxide (NO). Paradoxically, treatment with an anti-VEGF agent leads to an increase in prostacyclin (PGI₂), which may be driven by an upregulation in both cyclooxygenase (COX)-1 and COX-2. ET-1 may also contribute to the increase in PGI₂. The upregulation in PGI₂ and stimulation of its receptor, the prostanoid (IP) receptor, may act as a compensatory effect to counteract the kidney effects of ET-1/ETA receptor stimulation. However, very high levels of PGI₂ may then cause deleterious effects via stimulation of other prostanoid receptors such as the thromboxane (TP) or e-prostanoid (EP)₂₋₄ receptors [3]. Furthermore, there are **multikinase inhibitors** that target VEGFRs and other receptors involved in tumour vascularization. Multiple mechanisms could be involved in the pathogenesis of hypertension associated with these agents, such as abnormalities of the nitric oxide pathway, endothelial dysfunction and capillary rarefaction. Endothelial dysfunction accounts also for the development of proteinuria [1]. Moreover, these inhibitors have been associated with an increased incidence of electrolyte abnormalities, such as hypophosphataemia, hypocalcaemia and hyponatraemia.

Immune checkpoint inhibitors (ICIs)

Immune checkpoint inhibitors (ICIs) are primarily humanized or human IgG1 k or IgG4 k [4]. Kidney and liver dysfunction do not affect ICI clearance, they are not dialyzable and their half-life ranges from 7 to 27 days [5]. ICIs disrupt the normal immune regulatory checkpoints, leading to an activation of T cells against tumor cells. This can target kidney tissue, leading to an enhanced immune response and causing kidney injury. In addition, the production of autoantibodies and the formation of immune complexes can further exacerbate renal damage.

Immune checkpoint inhibitors (ICIs) are associated with a spectrum of renal immune-related adverse events (irAEs) including acute kidney injury (AKI), most commonly manifesting as acute interstitial nephritis (AIN), although glomerular disease and electrolyte disturbances have also been reported [6].

The most common types of glomerular lesions that have also been described that were pauci-immune glomerulonephritis/renal vasculitis (27%), podocytopathies, including minimal change disease and focal segmental glomerular sclerosis (24%), and C3 glomerulonephritis (11%) [7].

Although ICI use in patients with advanced chronic kidney disease (CKD) and end-stage kidney disease is not contraindicated, close monitoring is warranted, especially in patients with CKD, as the development of AKI may lead CKD progression and increased mortality [8].

Combination Therapy: anti-VEGF Agent and Immune Checkpoint Inhibitor

In recent years, anti-VEGF agent and ICI combination therapies have emerged rapidly in the oncologic field. The rationale for this combination lies in the **synergistic** effects of the two treatment modalities. Together, these treatments make the immune system more effective at attacking cancer cells [3]. There was a statistically significant higher rate of grade ≥ 3 proteinuria associated with the ICI-TKI combinations when compared to VEGF-TKI alone [9].

Management

While discontinuation of the **anti-VEGF Agent** (Table 1) results in significant reduction in proteinuria, persistence is common. Lowering of intraglomerular pressure may reduce protein excretion. There are no randomized controlled trials evaluating the benefit of agents, such as renin-angiotensin aldosterone system blockade in patients with proteinuria due to antiangiogenic agents [10]. Given the evidence that activation of the ET system is integral to the development of

hypertension and kidney damage during anti-VEGF therapy, it seems that targeting the downstream effects

of activation of the ET pathway may be a viable therapeutic option [3].

Table 1. Classification of anti-VEGF agents and immune checkpoint inhibitors

Drug class	Mechanism	Agents
Anti-VEGF agents	VEGF pathway inhibitors	Bevacizumab, Ramucirumab, Aflibercept
Multi-kinase inhibitors (VEGFR-targeted TKIs)	VEGFR tyrosine kinase inhibitors	Sunitinib, Sorafenib, Pazopanib, Axitinib, Cabozantinib, Lenvatinib, Regorafenib, Vandetanib, Tivozanib, Fruquintinib, Ponatinib
Immune checkpoint inhibitors (ICIs)	Anti-PD-1	Cemiplimab, Dostarlimab, Nivolumab, Pembrolizumab, Penpulimab, Retifanlimab, Tislelizumab, Toripalimab
	Anti-PD-L1	Atezolizumab, Avelumab, Cosibelimab, Durvalumab
	Anti-CTLA-4	Ipilimumab, Tremelimumab
	Anti-LAG-3	Relatlimab, nivolumab

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; LAG-3, lymphocyte-activation gene 3; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

The treatment of **ICI-AKI** (Table 1) depends on the severity and histopathologic subtype of injury (AIN, glomerular pathology). All patients require immediate cessation of drugs that are known to cause AIN (e.g., nonsteroidal anti-inflammatory drugs, PPIs, or antibiotics). For patients with stage 2 AKI or higher severity and strong clinical suspicion of ICI-AKI, immediate cessation of ICI therapy is advised, followed promptly by a plan for a kidney biopsy and the initiation of glucocorticoids. Alternate immunosuppressants such as infliximab [8] should be also used. In patients with ICI-glomerulonephritis it is suggested that nonsteroidal immunosuppressive therapy, such as rituximab, in combination with glucocorticoids [11] are to be used. Consequently, an appropriate prophylaxis for pneumocystis jirovecii pneumonia is advised for patients receiving immunosuppressive therapy. The pivotal decision to ICI **rechallenge** needs to be individualized, considering various factors, such as severity of initial ICI-AKI, other extrarenal irAEs, and the availability of alternative treatment options [8].

Conflict of interest statement. None declared.

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