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Onconephrology 2022: An Update

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Key Points:

Abstract:
Onconephrology is an upcoming and expanding subspecialty that deals with the intersections between hematology/oncology and nephrology. With the paradigm shift in the understanding of cancer immunobiology and mechanisms of onco-therapeutic drug toxicities, it is important for a nephrologist to have a sound understanding of this field. Over the last 5 years, there have been immense developments in our understanding of kidney related adverse events from various targeted, immuno and cellular-based therapies. Pathogenic mechanisms of electrolyte imbalance, hypertension (Onco-hypertension), and acute kidney injury from multiple forms of cancer therapies have been explored. Significant research has also been conducted in the field of transplant onconephrology. In this review, we have tried to assimilate the most recent updates in the last 2 years in this ever-growing and fascinating field.

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Onconephrology 2022: An Update

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Abstract

Onconephrology is an upcoming and expanding subspecialty that deals with the intersections between hematology/oncology and nephrology. With the paradigm shift in the understanding of cancer immunobiology and mechanisms of onco-therapeutic drug toxicities, it is important for a nephrologist to have a sound understanding of this field. Over the last 5 years, there have been immense developments in our understanding of kidney related adverse events from various targeted, immuno and cellular-based therapies. Pathogenic mechanisms of electrolyte imbalance, hypertension (Onco-hypertension), and acute kidney injury from multiple forms of cancer therapies have been explored. Significant research has also been conducted in the field of transplant onconephrology. In this review, we have tried to assimilate the most recent updates in the last 2 years in this ever-growing and fascinating field.
Introduction

Advances in hematology-oncology have led to improved long-term outcomes; however, it has become more important to understand the short- and long-term complications of cancer and antineoplastic therapies in the survivor. Cancer survivorship has led to increased chronic kidney disease and hypertension. This has paved a pathway for a new subspecialty of onconephrology. In this review, we shall update our readers on the recent studies and trials in various fields of onconephrology: Acute kidney injury (AKI), electrolyte disorders, onco-hypertension, glomerular disease, stem cell transplantation, paraprotein and amyloidosis, and transplant onconephrology.

Acute Kidney Injury Update

With the advances in anti-cancer treatment, such as new immunotherapies and other targeted therapies, more cancer patients are being evaluated in the nephrology services. Nephrologists taking care of these patients need to be updated on the kidney effects of anti-cancer treatments and how to manage them, with the ultimate goal of avoiding worsening kidney dysfunction and development of chronic kidney disease (CKD). Classical patterns of AKI seen in these patients are acute tubular injury, tubulointerstitial nephritis, vascular injury. Several glomerulopathies have also been described. Here we provide an update on AKI from anti-cancer therapies.

Immunotherapy Associated AKI

Immune check-point inhibitors (ICI) have dramatically strengthened the treatment of cancer. They work by directly inhibiting immune checkpoints allowing T-cells to remain in an active form and eliminate cancer cells. However, many immune-related adverse events have been described with these medications\(^1\), including ICI associated AKI. Most kidney immune-related adverse events are due to acute interstitial nephritis (AIN)\(^2\).

A large multi-center retrospective study collected over 400 cases of patients with AKI from immune checkpoint inhibitors \(^3\). These were compared to controls who received ICIs but
did not develop AKI. ICI-AKI occurred at 16 weeks (IQR 8-32). The use of proton pump inhibitor therapy (PPI), underlying low estimated glomerular filtration rate (eGFR), and presence of extra renal immune-related adverse events were risk factors. Acute interstitial nephritis was the most common kidney biopsy finding in 83% of patients. Treatment of ICI-AKI with steroids within 14 days following the diagnosis was associated with a higher odd of recovery, with early initiation favoring renal recovery. Of the 121 patients who were rechallenged, 16.5% developed recurrent ICI-AKI. There was no difference in survival among patients rechallenged versus those who were not, following ICI-AKI.

A recent meta-analysis examined the effects of AKI on outcomes in patients being treated with ICIs. This meta-analysis included 7 studies with a total of 3,767 patients demonstrating that ICI-associated AKI is of mild to moderate severity in most cases although incidence up to 43% for stage 2 AKI and up to 57% incidence for stage 3 AKI were reported. Kidney biopsy was performed in 43% of patients, where the most frequent finding was of tubulointerstitial disease. The presence and severity of AKI have an impact on all-cause mortality, and the absence of kidney recovery was noted to be a predictor of increased mortality. Even though these results are not definitive, they emphasize the need for clear management guidelines for AKI during the course of ICI therapy. Moreover, early recognition and proper management may improve the clinical outcome. The duration of steroid therapy has not been well defined. Single and multi-center data suggests that a shorter course of steroids with a quick taper is equivalent to a longer course for the treatment of ICI-induced AIN.

The addition of ICIs to standard chemotherapy has improved progression-free and overall survival in patients with metastatic nonsquamous non–small cell lung cancer (NSCLC) regardless of programmed death–ligand 1 expression. There has been concern for an increased risk of AKI in patients receiving combination therapy such as the triple therapy with pembrolizumab, pemetrexed, and platinum-based chemotherapy. Real-world data published recently showed that both groups (monotherapy and triple therapy) had a similar distribution of
AKI severity. However, AKI occurred early in the triple therapy group (105 days vs. 202 days). The kidney biopsy findings were more suggestive of tubular and interstitial damage than AIN alone\(^8\). Finally, several studies now confirmed the safe use of ICI in end stage kidney disease (ESKD) patients, as they had similar incidence of immune related adverse events when compared to the general population. This is likely due to the main mechanism of ICI clearance, through proteolytic catabolism and receptor mediated endocytosis.\(^9-11\).

 Ideally, a non-invasive test to predict a kidney-related adverse immune event would be an invaluable resource in these patients. A recent novel study by Isik et al reviewed the role of commonly available laboratory tests, such as C reactive protein (CRP) and urine retinol binding protein (RBP), in predicting ICI related-AKI\(^12\). Elevated CRP with an elevated urine RBP/creatinine were helpful in identifying patients with ICI-related AKI. A more recent preprint study showed that soluble interleukin-2 receptor(sIL-2R) level in peripheral blood was significantly higher in patients with ICI related nephritis compared to ICI-treated controls and hemodynamic AKI controls\(^13\). A sIL-2R cut-off point of 1.75-fold upper limit of normal was highly diagnostic of ICI-nephritis (AUC >96\%) when compared to either ICI-treated or hemodynamic AKI controls. By peripheral blood flow cytometry analysis, lower absolute CD8+ T cells, CD45RA+CD8+ T cells, memory CD27+ B cells, and expansion of plasmablasts were prominent features of ICI-nephritis compared to ICI-treated controls. Another emerging biomarker is urine TNF-alpha as its level was significantly elevated in ICI-nephritis when compared to other causes of AKI\(^14\). TNF-α in conjunction with specific T-cell responses contribute to AKI-ICI injury and could potentially serve as targets for therapeutic intervention as well as potential biomarkers.

 Imaging biomarkers using computerized tomography (CT) and positron emission tomography (PET) have also been investigated recently in a larger cohort at a single center. Bilateral increase in kidney size, new/increasing perinephric stranding, and bilateral wedge-
shaped hypoenhancing cortical foci can occur in ICI–related nephritis. On PET-CT, a diffuse increase in radiotracer uptake throughout the renal cortex and a decrease in radiotracer activity in the renal pelvis can be seen\(^{15}\).

**Pseudo AKI from Novel Molecularly Targeted Agents**

Three classes of agents, namely mesenchymal-epithelial transition (MET) tyrosine kinase inhibitors, inhibitors of poly-adenosine diphosphate ribose polymerase (PARP), and the cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have been newly associated with pseudo-AKI (an asymptomatic rise in serum creatinine).\(^{16}\) The underlying mechanisms of pseudo-AKI are associated with inhibition of renal transporters such as organic cation transporter-2, multidrug and toxin extrusion-1 (MATE-1), and MATE2-K\(^{17}\) leading to a reversible increase in serum creatinine (SCr)\(^{18,19,20,21}\). However, kidney biopsy-proven cases of acute tubular injury have also been reported with CDK 4/6 inhibitors recently\(^{22}\).

Differentiating “pseudo-AKI” from true AKI can be challenging. Simultaneous measurement of SCr, kidney iothalamate clearance, and/or eGFR based on cystatin C level may help distinguish between the two entities\(^{23}\). **Table 1** summarizes updated kidney toxicities with conventional and new anticancer agents.

**Novel mechanisms of tubular injury for chemotherapy**

Two studies highlight the emerging role of heme and heme metabolism in AKI from two chemotherapy agents. Bai *et al.* analyzed whether the BRAF inhibitor vemurafenib directly causes renal tubular epithelial cell (RTEC) injury *in vitro*\(^{24}\). In comparison with the control mice, proximal tubule–specific BRAF knockout mice showed no significant changes in blood urea and creatinine levels or histology before and after vemurafenib administration, indicating the possibility of a BRAF-independent mechanism in vemurafenib-induced nephrotoxicity. Previous chemical proteomic studies suggested that vemurafenib, but not other BRAF inhibitors, inhibits
ferrochelatase (FECH)\textsuperscript{25}. FECH is a mitochondrial protein that inserts ferrous ions into a precursor protoporphyrin IX to form protoheme (heme b), which is the final step of heme synthesis.\textsuperscript{26} The authors found a significant reduction in FECH activity and heme levels and mitochondrial dysfunction in vemurafenib-treated RTECs. \textit{In vivo} analysis showed that FECH was more abundantly expressed in RTECs than in other renal cells in the normal condition and that the activity of FECH heme levels was downregulated and caspase activity was upregulated in RTECs after vemurafenib treatment. On the basis of these data, they put forth that vemurafenib-induced RTEC injury can be mediated by FECH inhibition and subsequent heme depletion. Furthermore, the \textit{in vivo} knockdown of FECH did not influence normal renal function but hastened vemurafenib-induced nephrotoxicity. These data suggest that vemurafenib-induced nephrotoxicity is BRAF independent, and can, in part, be explained by reduced FECH activity. Hemopexin, a heme scavenging protein, accumulates in the kidneys during AKI. In a recent study, the authors found an accumulation of hemoglobin and hemopexin in the kidneys localized to the proximal tubules in mice with cisplatin toxicity\textsuperscript{27}. There was increased kidney expression of kidney injury molecule-1 and heme oxygenase-1 (an indicator of oxidative stress) in hemopexin wild type compared with knockout mice in both models of AKI. Co-incubation of hemopexin with hemoglobin resulted in hemoglobin deposition and exaggerated hemoglobin-induced injury. Deferoxamine, an iron chelator, and ferrostatin-1, a ferroptosis inhibitor, inhibited this deleterious effect of hemoglobin and hemopexin in proximal tubular cells, implicating iron toxicity in the mechanism of hemopexin-mediated injury in cisplatin mediated AKI. Furthermore, the protective effect of deferoxamine in cisplatin-induced AKI was apparent in hemopexin wild type, but not in hemopexin knockout mice.

\textbf{Electrolyte Disorders Update}

\textit{Immunotherapy associated electrolyte disorders}
Immune checkpoint inhibitors therapy can lead to hyponatremia by several mechanisms, with the syndrome of inappropriate antidiuresis being the most common. Endocrine causes of hyponatremia are rare. Hypokalemia is also common and is associated with both proximal and distal renal tubular acidosis. Hypercalcemia associated with immune checkpoint inhibitors has led to some interesting observations, including immune checkpoint inhibitor–induced parathyroid hormone–related peptide production, sarcoid-like granulomas, and hyper progression of the disease. Hypocalcemia and hyperphosphatemia may be seen with immune checkpoint inhibitors–induced tumor lysis syndrome. Chimeric antigen receptor T cell (CAR-T) therapy–associated electrolyte disorders are also common. This is associated chiefly with hyponatremia, although other electrolyte abnormalities can occur. Table 2 summarizes all novel immunotherapy-associated electrolyte disturbances recently noted in case series and case reports.

**Tumor Lysis Syndrome**

Tumor Lysis Syndrome (TLS) is an oncolgical emergency. It occurs secondary to anti-cancer therapies in patients with high tumor burden or spontaneously. Lysis of tumor cells leads to the release of intracellular ions and metabolites into the systemic circulation, precipitating hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia. While most of the literature supported a crystalopathy-related AKI as the patho-mechanism, a recent study postulated a novel pathophysiologic model through which AKI is associated with endothelial dysfunction from high levels of extracellular histones. This animal study proved that extracellular histones are released in vast amounts during TLS, causing a profound endothelial injury in the mouse model. The mechanisms of histone-mediated damage implicate endothelial cell activation mediated by Toll-like receptor 4. In addition, TLS has now been associated with novel agents such as the B-cell lymphoma 2 inhibitor venetoclax, the monoclonal antibody
obinutuzumab\textsuperscript{32,33}, and even immune checkpoint inhibitors. Although, data on such associations are related to case reports and case series\textsuperscript{28,32,33}.

**Hyponatremia**

Selinexor is a selective inhibitor of the nuclear export protein exportin 1 (XPO1); it is approved in combination with dexamethasone for the treatment of multiply relapsed or refractory multiple myeloma and for relapsed/refractory diffuse large B cell lymphoma. Selinexor can cause hyponatremia with incidence ranges from 7 to 26\%\textsuperscript{34}. It is a common grade 3 or 4 adverse event (serum sodium level, <130 mmol per liter) in 22\% of the patients\textsuperscript{35}. The mechanism of hyponatremia is not yet elucidated. The observed hyponatremia is likely related to multiple factors, comorbidities, other medications, and selinexor side effects non-kidney related; nausea and volume depletion, and possible unidentified kidney factor\textsuperscript{36}.

Immune checkpoint inhibitors and CAR-T therapy have also been associated with hyponatremia (Table 2)\textsuperscript{37}. While initially thought to be related to endocrinopathies, syndrome of inappropriate antidiuresis (SIAD) is the most common mechanism for hyponatremia\textsuperscript{38,39}.

**Magnesium disorders in cancer patients.**

Hypomagnesemia is another crucial electrolyte disorder in cancer patients, and the causes may differ among patients depending on nutritional status and specific cancer therapies. This review will focus on two significant cancer therapies: Platinum-based chemotherapy and cetuximab, an epidermal growth factor receptor (EGFR) monoclonal antibody, induced hypomagnesemia.

Platinum-based chemotherapy, in particular cisplatin, is associated with hypomagnesemia. The main mechanism of hypomagnesemia in these patients is renal magnesium wasting due to direct toxicity from an intracellular accumulation of cisplatin, ultimately causing tubular cell injury\textsuperscript{40}. Cetuximab-induced hypomagnesemia is also secondary
to primary renal magnesium wasting, mechanistically from an inhibition of the basolateral EGFR, which prevents the transcellular magnesium reabsorption via the TRPM6 Mg channels\(^{41}\). Sodium glucose transporter 2 (SGLT2) inhibitors have been used in patients with refractory hypomagnesemia above and beyond the magnesium replenishment \(^{42,43}\). A meta-analysis showed an increased serum Mg levels in patients by 0.15-0.24mg/dl, but the exact mechanism of this effect is unknown \(^{44}\). A plausible explanation of improvement in Mg\(^{2+}\) levels is by increased Mg\(^{2+}\) absorption in the intestine or reabsorption in the kidney, possibly by enhancing TRPM6 mediated transport in the intestine and/or the kidney\(^{45}\).

**Onco-hypertension Update**

The topic of hypertension (HTN) in cancer patients or “onco-hypertension” has gained increasing attention over the past years \(^{46}\). Interestingly, the relationship has been portrayed as bidirectional. HTN has been noticed with several classes of drugs, including conventional agents such as cisplatin \(^{47,48}\). The topic gained much attention with the introduction of more contemporary targeted therapies such as vascular endothelial growth factor (VEGF) inhibitors\(^{49}\). This section focuses on the newest anti-cancer agents inducing HTN.

**VEGF Signaling Pathway Inhibitors (VEGFi) Induced HTN**

VEGF signaling pathway inhibitors are the prototype of anti-cancer drug-induced hypertension (Figure 1), observed in 20-90% depending on VEGFi type and blood pressure (BP) definitions \(^{49,50}\). Risk factors for the development of HTN include a previous history of HTN, age ≥ 60 years, body mass index (BMI) ≥ 25 kg/m\(^2\), concurrent use of more than one VEGFi medication, as well as tumor type such as renal cell carcinoma (RCC) \(^{49,51}\). Not much has been reported on the management of VEGFi induced HTN in the last few years. A recent review summarizes these
findings. Table 3. summarizes anti-VEGF signaling pathway agents kidney adverse events. 

The mechanism of VEGFi induced hypertension is shown in Figure 1.

**Bruton’s Tyrosine Kinase Inhibitors Induced HTN**

Bruton tyrosine kinase (BTK) inhibitors such as Ibrutinib have revolutionized the management of chronic lymphocytic leukemia and mantle cell lymphoma. However, long-term treatment is associated with an increased risk of developing cardiovascular complications, including atrial fibrillation and HTN. In this systematic review with meta-analysis of randomized controlled trials, the relative risk of HTN with ibrutinib therapy was 2.82 (95%CI 1.52-5.23), with a range of HTN incidence from 18 to 75%. The mechanisms of BTK inhibitor-induced HTN are unclear, but a decrease in heat shock protein 70 signaling pathways and inhibition of phosphatidylinositol 3-kinase-dependent and nitric oxide (NO) downregulation have been postulated. So far, data indicate a lower incidence of HTN with second-generation BTK inhibitors such as acalabrutinib.

**Phosphatidylinositol-3 kinase (PI3K) Inhibitors Induced HTN**

Toxicities from small-molecule PI3K inhibitors depend on their PI3K isozyme specificity. Copanlisib is a pan-PI3K with nonselective blockage of PI3K signaling approved for the third-line treatment of follicular non-Hodgkin lymphoma. HTN occurs primarily during infusion in almost 30% of the patients, and it is transient, resolving within 24hrs, and usually less prominent with subsequent cycles. The mechanism is likely related to targeting the PI3K-α isoform. PI3Kα is the isoform predominantly mutated in cancer, and studies have shown that selective inactivation of this isoform is enough to block PI3K/AKT signaling in response to different growth factors stimuli. Idelalisib and duvelisib target the PI3Kp110δ isoform and are also known to induce hypertension.
Immune checkpoint inhibitors and HTN

Recently a systematic review and meta-analysis was performed by Minegishi et al to look at the incidence of HTN from immune checkpoint inhibitors. Thirty-two randomized controlled trials with around 19,000 patients included in the meta-analysis did not show any increased association with short term risk of HTN in patients with cancer and the association was similar regardless of concurrent treatment with other anticancer medications.  

Other Miscellaneous Anti-Cancer Agents associated with HTN

BRAF/MEK inhibitors are used in the treatment of BRAF-mutant melanoma and colorectal cancer, with HTN being the most common cardiovascular adverse event reported with these drugs. HTN occurs in approximately 14% and 20% of patients treated with BRAF inhibitor monotherapy and BRAF/MEK inhibitors, respectively. The mechanism may be related to decrease of nitric oxide bioavailability, causing vasoconstriction and, consequently, HTN. Poly adenosine diphosphate ribose polymerase inhibitors (PARPIs) have been used to treat ovarian cancer, and HTN has developed in 12-20% versus 1-6% of placebo. However, the mechanism leading to HTN is not entirely understood. The anti-androgens, abiraterone, and enzalutamide, used for prostate cancer, have been associated with the development of all-grade HTN in 26% and 11%, respectively. Abiraterone inhibits cytochrome P450 enzymes leading to the accumulation of mineralocorticoid precursors and contributing to its prohypertensive effects. However, the mechanisms underlying enzalutamide-induced HTN remain unclear. Aromatase inhibitors such as anastrozole used for estrogen-positive (ER+) breast cancer have been associated with higher rates of HTN and cardiovascular events.  

Glomerular Diseases and Cancer Update

There is an established relationship between glomerular disease and cancer, associated with both solid and hematological malignancies, and during the course of cancer treatment. Diverse
patterns of glomerular injury have been observed and described in the literature. In recent years, we have seen an increased discovery of many new antigens associated with membranous nephropathy (MN). This review aims to provide an update on MN and the new antigens associated with cancer.

Thrombospondin type-1 domain-containing 7A (THSD7A) accounts for 1% to 3% of MN cases in western countries. It is also overexpressed in certain malignancies such as gall bladder and endometrial cancers. Strong THSD7A staining has also been seen in prostate, breast, kidney, and colorectal cancers. Autoantibodies to neural epidermal growth factor-like 1 (NELL-1) protein is another recent addition to the list of antigens implicated in MN. NELL-1–associated MN was identified in approximately 16% of PLA2R-negative MN cases without any identifiable secondary cause. The current literature suggests a connection between NELL-1 associated MN and malignancy. In addition, 21.4% of patients with Protocadherin 7 (PCDH7) associated MN had a malignancy. The precise pathology and antigens have not been clearly defined. Figure 2 summarizes the various ways one can differentiate primary versus malignancy associated MN.

New glomerular diseases have now been reported in association with ICI as well. In an analysis of all published case reports and case series of glomerular pathology findings associated with immune checkpoint inhibitors, several lesion types were observed, with the most frequent being pauci-immune glomerulonephritis (GN) and renal vasculitis (27%), podocytopathies (24%), and complement 3 GN (C3GN; 11%). Since then, several other glomerular pathologies have been reported and observed (unpublished) in clinical practice such as MN, mesangioproliferative glomerulonephritis and other podocytopathies. (Figure 3). Treatment of glomerular diseases associated with ICI is challenging.

**HSCT-related kidney disease update**
Kidney disease post-HSCT includes acute kidney injury (AKI) as well as chronic kidney disease (CKD), both of which result in high morbidity and mortality. Below are two novel concepts noted in the literature on kidney diseases associated with HSCT.

“Haplostorm” associated AKI

The use of haploidentical donors has expanded the number of patients eligible for this curative therapy. Patients who undergo T-cell replete peripheral blood haploidentical hematopoietic transplantation (Haplo-HSCT) have an additional risk for the development of AKI termed as “Haplostorm associated AKI”. Haplostorm is a cytokine release syndrome (CRS) seen within 14 days of transplantation. It is characterized by fever, rash, diarrhea, vascular leak, hypotension, and multisystem organ dysfunction, including acute kidney injury. The high incidence of cytokine release syndrome seen in haploidentical peripheral blood transplants as compared to bone marrow transplants is due to the presence of 8 fold more lymphocytes in peripheral blood allografts. In a small retrospective study spanning 13 years of a total of 55 cases of confirmed haplostorm, 7 were found to have haplostorm associated with AKI (13%). All these patients suffered from severe cytokine release syndrome characterized by hypotension with pressor support requirement as well as hypoxemia requiring supplemental oxygen. In another study by Imus et al. of a total of 146 patients who underwent Haplo-HSCT, severe CRS was seen in 25 patients (17%) of which 12 patients suffered severe AKI requiring hemodialysis. Management of these patients is challenging with a focus on supportive therapy, steroid use, and anti IL-6 therapy e.g., Tocilizumab. Nephrologists need to be aware of this novel cause of AKI post HSCT in the special situation of a haplo-identical HSCT.

Novel Antigens associated with HSCT associated Nephrotic Syndrome
The development of glomerular diseases post HSCT is considered by many to represent the kidney manifestation of graft versus host disease (GVHD) \(^{88}\). The most common pathological lesion seen is MN, followed by minimal change disease. While PLA2R antigen-associated membranous GN has been reported in some HSCT recipients \(^{89,90}\), most cases are PLA2R negative, and the target antigen remains unknown. Recently, Nasr et al \(^91\) reported 5 patients with membranous nephropathy and extensive tubular basement membrane deposits following allogeneic HSCT who presented with acute tubular injury and tubulointerstitial inflammation. Proteomic analysis was negative for routine antigens such as THSD7A, EX 1/2, NELL-1, SEMA3B. Only one out of 5 patients tested positive for PLA2R, while the identity of the target antigen in the remaining cases remained unknown. NELL-1 associated membranous GN following HSCT has also been described \(^92\). A study published by Sethi et al \(^93\) revealed a novel protein, protocadherin (FAT1), which was detected by microdissection and mass spectrometry in patients with HSCT-associated membranous nephropathy, all of whom were PLA2R antigen negative. The FAT cadherins comprise four members, FAT1–FAT4, and all are large transmembrane proteins of 500–600 kD \(^94\). The biological function of FAT cadherins is not well understood. FAT1 recessive mutations in humans have been associated with glomerulotubular nephropathy exhibiting extensive podocyte foot process effacement and resulting in steroid-resistant nephrotic syndrome \(^95\). The authors postulate that a somatic/previous hidden FAT1 mutation may cause an immune response as a consequence of GVHD in most of these cases \(^93,96\).

Paraproteinemia and Amyloidosis update

**Multiple myeloma and other forms of monoclonal gammopathy of renal significance (MGRS)**

The new International Kidney and Monoclonal Gammopathy Research Group (IKMG) consensus definition of MGRS includes all B cell or plasma cell proliferative disorders that produce a nephrotoxic monoclonal immunoglobulin. A recent study demonstrated that 98% of
patients with cast nephropathy (CN) diagnosis presented with serum free light chains (sFLC) levels > 500 mg/L. As per the International Myeloma Working Group (IMWG) CN was characterized by the presence of histopathological features or the involved sFLC of more than 1500 mg/L. A recently published retrospective French study outlined a distinct subset of patients with MGRS who develop thrombotic microangiopathy (TMA). Prognostically, this is an important phenotype, with 70% of patients needing dialysis at the disease onset and median renal survival being 20 months. A Chinese single-center large cohort study analyzed kidney biopsy specimens of patients with MGRS who underwent a kidney biopsy (N=700). Thirty eight percent of patients had some form of MGRS lesions (63%-Ig associated amyloidosis, 9% monoclonal immunoglobulin deposition disease, 8%-TMA). Membranous nephropathy (40%) was the most common non-MGRS lesion. The above recent studies expand the various known pathologies seen with MGRS.

Proteasome-inhibitor based therapies have had a major impact on the survival of patients with both newly diagnosed and relapsed myeloma. A recently published multicenter trial compared double [bortezomib + dexamethasone (BD)] vs triple [cyclophosphamide + bortezomib + dexamethasone (C-BD)] regimens in patients with MM and AKI from cast nephropathy. The study did not show any benefit of C-BD compared to BD on kidney recovery of patients with CN not needing dialysis. The therapeutic drugs for MM and MGRS themselves are not devoid of kidney injury risk. The primary objective in the treatment of MGRS is preserving kidney function, and the treating physician should be mindful of the nephrotoxic effects of the various agents used. In a setting of plasma cell clones the best results are achieved using proteasome-inhibitor based regimens. Other therapies are melphalan followed by autologous HSCT in patients with monoclonal Ig deposition disease (MIDD), anti-CD-38 monoclonal antibody, daratumumab for proliferative glomerulonephritis with monoclonal deposits (PGNMID) and rituximab-based therapy for patients with B cell clone which express
CD-20. Daratumumab may become standard therapy for several diseases with the MGRS phenotype based on its recent success in a pilot study for PGNMID.

Therapies available for AL amyloidosis are high dose melphalan followed by autologous stem cell transplant, melphalan-dexamethasone combination, CyBorD (cyclophosphamide-bortezomib-dexamethasone), bortezomib-melphalan-dexamethasone combination and daratumumab (anti CD-38 antibody). In a recent RCT with newly diagnosed AL amyloidosis, the addition of daratumumab to CyBorD was associated with higher frequencies of hematological complete response and survival.

Extracorporeal therapies utilized for the removal of sFLC are plasma exchange (PLEX) and high cut-off (HCO) dialysis. A Canadian study demonstrated no conclusive evidence of PLEX in reducing composite outcomes of death, dialysis dependence or eGFR < 30 mL/min per 1.732m² at 6 months. Multiple Myeloma and Renal Failure Due to Myeloma Cast Nephropathy (MYRE) and EuLITE (The European Trial of Free Light Chain Removal by Extended Hemodialysis in Cast Nephropathy) utilized HCO dialysis membranes to facilitate sFLC removal and study dialysis primary endpoint of independence at 3 months. Both trials did not demonstrate a significant difference between treatment and control arm. Based on the findings of the trials, the utility of HCO dialysis and PLEX for decreasing sFLC burden to improve kidney outcomes remains elusive and cannot be routinely recommended.

**Transplant Onconephrology Update**

The field of transplant onconephrology has now been increasingly recognized. Recent advancements in cancer treatment have changed the landscape of pre and post-transplant management however, there is an unmet clinical need to improve patient outcomes.
**Immunotherapy in Kidney Transplant Recipients.**

A multicenter observational study investigated the efficacy and safety of ICIs in kidney transplant recipients\(^{112}\). The estimated risk of acute rejection was 42\%, with median ICI to rejection time being 24 days. The rejection risk was lower if the patients were on a higher number of immunosuppressants (e.g., 3 agent immunosuppression) and mTOR inhibitors. In patients with advanced cutaneous squamous cell carcinoma (cSCC) the overall survival in those receiving ICIs was significantly longer than that of historical cohorts of advanced cSCC who did not receive ICIs. Another phase 1 multicenter study (N=17), showed that ongoing immunosuppression along with nivolumab showed less chance of rejection and no change in response to the cancer\(^{113}\). Both studies conclude that kidney transplant recipients can be given ICIs with ongoing immunosuppression to prevent rejection and no changes in cancer remission.

Several clinical trials are underway to investigate immunosuppression strategies in kidney transplant recipients. One approach is to continue tacrolimus (NCT03816332) for those with skin cancer (cSCC, melanoma, basal cell carcinoma, Merkel cell carcinoma) treated with ipilimumab and/or nivolumab. Another approach includes a combination of mTOR inhibitor and dynamic steroid dosing for cSCC treated with cemiplimab (NCT04339062). In this study, the patients receive mini prednisone pulse synchronizing with the infusion, modified from a previously reported approach\(^{114}\). However, acute rejection can still occur in patients on kidney replacement therapy with previously failed kidney transplants. In these cases, patients developed allograft pain and fever 2-4 weeks after the first cycle of ICI therapy, owing to allograft intolerance syndrome\(^9\).

*Can a patient with myeloma and light/heavy chain amyloidosis get a kidney transplant?*

Patients with ESKD from MM have poor outcomes on dialysis. MM has traditionally been a contraindication to kidney transplantation, owing to reported high relapse rates and high risk of
allograft loss\textsuperscript{9,115}. Data on outcomes of patients with MM and amyloidosis-induced ESKD getting a kidney transplant were limited to case reports and case series\textsuperscript{116}. A recent retrospective study of the UNOS/OPTN dataset (2006-2018) compared patient and graft outcomes of kidney transplant recipients with ESKD due to plasma cell dyscrasias (PCD) vs other causes\textsuperscript{117}. Among 168,369 first kidney transplants adult recipients, 0.22-0.43\% per year (a very small proportion) had plasma cell dyscrasias as the cause of ESKD. The plasma cell dyscrasias group had worse survival than the non-plasma cell dyscrasias group for both living and deceased donor types [adjusted hazard ratio [aHR]: 2.24 (95\% CI 1.67-2.99) and 1.40 (95\% CI 1.08-1.8)]. The plasma cell dyscrasias group had worse survival than the diabetes group, but only among living donor types [aHR: 1.87 (95\% CI 1.37-2.53) vs 1.16. (95\% CI 0.89-1.2)] Graft survival in patients with the plasma cell dyscrasias was worse than non-plasma cell dyscrasias in both living and deceased donor types [aHR 1.72 (95\% CI 1.91-2.56) vs 1.30. (95\% CI 1.03-1.66)] Patient and graft survival were worse in amyloidosis but not statistically different in multiple myeloma, compared to the non-plasma cell dyscrasias group. The comparison of outcomes of patients with ESKD due to plasma cell dyscrasias in the context of other causes of ESKD will guide future eligibility criteria for patients with PCD to receive kidney transplantation, particularly at the level of transplant centers.

Another study looked at AL amyloidosis and kidney transplantation\textsuperscript{118}. This multicenter observational study from five countries includes 237 patients with AL amyloidosis who underwent renal transplantation between 1987 and 2020. With a median follow-up of 8.5 years, the median overall survival from renal transplantation was 8.6 years and was significantly longer in patients with complete and very good partial hematologic responses (CR + VGPR) compared to less than VGPR (9 versus 6.8 years; HR: 1.5, \(P=0.04\) [95\% CI: 1–2.1]) at renal transplantation. Median graft survival was 7.8 years and was better in the CR + VGPR group (8.3 vs 5.7 years, HR: 1.4, \(P=0.05\) [95\% CI: 1–2]). The frequency and time to amyloid recurrence in the graft were also lower (16\% vs 37\%, \(p=0.01\)) and longer (median time not
achieved vs 10 years, \( p = 0.001 \) in the CR + VGPR group. Comparing CR vs. VGPR there was no difference in overall or graft survival. Although 69 patients (29%) experienced hematologic relapse, the treatment effectively prevented graft loss in the majority (87%). Kidney transplantation in selected AL amyloidosis patients is associated with extended overall and renal graft survival. Patients with hematologic CR or VGPR have the most favorable outcomes, and these patients should be considered for kidney transplantation. Similar studies in other forms of paraprotein mediated diseases receiving more conventional novel treatments and then getting a kidney transplantation are required.

**Conclusion**

Since the inception of the field of onconephrology over a decade ago, original investigations related to many sections in this field have increased. In the last few years, we saw increasing recognition of novel agents causing pseudo-AKI. We learned about novel agents causing HTN and are moving the glomerular disease field forward with specific cancer markers for paraneoplastic MN. In addition, our understanding of immunotherapy-related AKI and risk factors has been supplemented with the new wealth of data. The field of transplant onconephrology has seen recent advancements in the treatment of patients on immunotherapy and how to navigate the challenges of a patient with paraproteinemia and ESKD now needing a kidney transplant. The field of onconephrology is currently ripe for more ongoing original investigations.

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**Author Contributions**

Marco Bonilla: Conceptualization; Formal analysis; Supervision; Validation; Visualization; Writing - original draft; Writing - review and editing. Prakash Gudsoorkar: Writing - original draft; Writing - review and editing. Rimda Wanchoo: Writing - review and editing. Sandra Herrmann: Writing - review and editing. Kenar Jhaveri: Data curation; Validation; Visualization; Writing - original draft; Writing - review and editing.
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Table 1. Summarized kidney adverse effects from anticancer therapies.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug name</th>
<th>Mechanism of Injury</th>
<th>Kidney effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum based</td>
<td>Cisplatin, Carboplatin, Oxaliplatin.</td>
<td>Platinum-DNA adducts mediate arrest of cell cycle, initiate apoptosis. ATP depletion.</td>
<td>ATI, renal magnesium wasting, proximal tubulopathy, NDI</td>
</tr>
<tr>
<td>Antimetabolite</td>
<td>Methotrexate</td>
<td>Intratubular crystal formation. Afferent arteriolar constriction</td>
<td>Crystal nephropathy, ATI</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Endothelial injury</td>
<td>TMA, HTN</td>
<td></td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Unknown</td>
<td>ATI, Chronic interstitial fibrosis, proximal tubulopathy, NDI</td>
<td></td>
</tr>
<tr>
<td>Alkylating agent</td>
<td>Cyclophosphamide</td>
<td>Toxic metabolite, acrolein</td>
<td>hemorrhagic cystitis</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Toxic metabolite, chloroacetaldehyde</td>
<td>ATI, proximal tubulopathy, NDI</td>
<td></td>
</tr>
<tr>
<td>Melphalan</td>
<td>Increase ADH release</td>
<td>SIADH</td>
<td></td>
</tr>
<tr>
<td>Nitrosoureas</td>
<td>Alkylation of tubular cell proteins</td>
<td>Chronic interstitial nephritis</td>
<td></td>
</tr>
<tr>
<td>Antitumor antibiotics</td>
<td>Mitomycin C</td>
<td>Endothelial injury</td>
<td>TMA, HTN</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>Bevacizumab</td>
<td>Endothelial injury</td>
<td>TMA, HTN, ATI</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>Sorafenib, sunitinib, axitinib, pazopanib, lenvatinib.</td>
<td>Endothelial injury, podocyte injury.</td>
<td>ATIN, ATI, TMA, FSGS</td>
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<tr>
<td>BCR-ABL tyrosine kinase inhibitor</td>
<td>Imatinib, dasatinib.</td>
<td>Tubular injury, endothelial injury</td>
<td>ATI, TMA</td>
</tr>
<tr>
<td>BRAF inhibitors</td>
<td>Vemurafenib, dabrafenib</td>
<td>Tubular injury, ERK activation.</td>
<td>ATIN, ATI</td>
</tr>
<tr>
<td>BCL-2 inhibitors</td>
<td>Venetoclax</td>
<td>Tubular injury</td>
<td>AKI, TLS</td>
</tr>
<tr>
<td>ALK inhibitors</td>
<td>Crizotinib, lorlatinib, alectinib</td>
<td>Inhibition of creatinine secretion, renal arteriolar myocyte vacuolization</td>
<td>Pseudo-AKI, ATIN, ATI, kidney cyst, podocytopathies</td>
</tr>
<tr>
<td>CDK4/6 inhibitors</td>
<td>Palbociclib, ribociclib</td>
<td>Inhibit MATE1 and MATE2 transporters</td>
<td>Pseudo-AKI, ATI</td>
</tr>
<tr>
<td>PARP inhibitors</td>
<td>Olaparib, talazoparib</td>
<td>Inhibition of creatinine secretion</td>
<td>Pseudo-AKI</td>
</tr>
<tr>
<td>MET tyrosine kinase</td>
<td>Capmatinib, tepotinib</td>
<td>Inhibition of creatinine</td>
<td>Pseudo-AKI</td>
</tr>
<tr>
<td>EFGFR monoclonal antibodies</td>
<td>Cetuximab, panitumumab</td>
<td>inhibition of EGFR signaling at the DCT</td>
<td>Renal magnesium wasting</td>
</tr>
<tr>
<td>-----------------------------</td>
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<tr>
<td>mTOR inhibitors</td>
<td>Everolimus</td>
<td>Decrease cubilin and megalin, VEGF inhibition</td>
<td>ATI, podocytopathies</td>
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<tr>
<td>Protease inhibitors</td>
<td>Bortezomib, carfilzomib</td>
<td>Endothelial injury, autoantibody formation</td>
<td>TMA, HTN</td>
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<td>Bruton tyrosine kinase</td>
<td>Ibrutinib</td>
<td>Endothelial injury</td>
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<tr>
<td>inhibitors</td>
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<tr>
<td>XPO inhibitor</td>
<td>Selinexor</td>
<td>volume depletion</td>
<td>hemodynamic AKI, hyponatremia</td>
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<td><strong>Immunotherapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR-T therapy</td>
<td>Axicabtagene ciloleucel, Idecabtagene vicleucel, brexucabtagene autoleucel, Tisagenlecleucel.</td>
<td>Systemic hyperinflammatory state. Ischemic injury</td>
<td>ATI, hemodynamic mediated AKI</td>
</tr>
<tr>
<td>CTLA-4 inhibitor</td>
<td>Ipilimumab, tremelimumab</td>
<td>Tubular injury, endothelial injury, podocyte injury</td>
<td>ATIN, ATI, MCD, lupus-like GN, necrotizing GN, TMA</td>
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<tr>
<td>PD-1 inhibitors</td>
<td>Pembrolizumab, cemiplimab, nivolumab</td>
<td>Tubular injury, endothelial injury, podocyte injury</td>
<td>ATIN, ATI, MCD, IgA nephropathy, FSGS, Necrotizing GN, Amyloidosis, Immune-complex mediated GN</td>
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<td>PDL-1 inhibitor</td>
<td>atezolizumab, avelumab, durvalumab</td>
<td>Tubular injury</td>
<td>ATIN, ATI</td>
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</table>

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Disorder</th>
<th>Cancer immunotherapy</th>
<th>Mechanism</th>
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<tr>
<td>Sodium</td>
<td>Hyponatremia</td>
<td>Immune checkpoint inhibitors</td>
<td>Hypophysitis</td>
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<td></td>
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<td>Adrenalitis</td>
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<td></td>
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<td>Thyroiditis</td>
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<td>SIADH</td>
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<td></td>
<td>CAR-T cell therapy</td>
<td>CRS</td>
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<td></td>
<td></td>
<td></td>
<td>Hypovolemia</td>
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<td>Potassium</td>
<td>Hypokalemia</td>
<td>Immune checkpoint inhibitors</td>
<td>GI losses (Gastritis, Colitis)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Distal and proximal RTA</td>
</tr>
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<td></td>
<td></td>
<td>CAR-T cell therapy</td>
<td>Renal tubular defect</td>
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<td>Calcium</td>
<td>Hypocalcemia</td>
<td>Immune checkpoint inhibitors</td>
<td>Autoimmune hypoparathyroidism</td>
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<td></td>
<td></td>
<td>TLS</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia</td>
<td>Immune checkpoint inhibitors</td>
<td>Hypophysitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thyroid disorders</td>
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<td></td>
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<td></td>
<td>ICI-related PTHrP</td>
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<td></td>
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<td></td>
<td>Hyper-Progression of disease</td>
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<td></td>
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<td></td>
<td>Sarcoid like granulomas</td>
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<tr>
<td>Phosphorous</td>
<td>Hypophosphatemia</td>
<td>Immune checkpoint inhibitors</td>
<td>Proximal tubulopathy</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>GI losses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAR-T cell therapy</td>
<td>Unknown (hypotheses GI or kidney losses)</td>
</tr>
<tr>
<td></td>
<td>Hyperphosphatemia</td>
<td>Immune checkpoint inhibitors</td>
<td>TLS</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Hypomagnesemia</td>
<td>Immune checkpoint inhibitors</td>
<td>GI losses, inflammatory diarrhea.</td>
</tr>
</tbody>
</table>

CAR-T: Chimeric antigen receptor T cells; CRS: Cytokine Release Syndrome; GI: Gastrointestinal; ICI: immune checkpoint inhibitor; PTHrP: parathyroid related peptide; RTA: Renal tubular acidosis; SIADH: Syndrome of inappropriate antidiuretic hormone; TLS: Tumor Lysis Syndrome.
<table>
<thead>
<tr>
<th>Anti-VEGF Agents Subclasses</th>
<th>Drugs</th>
<th>Indications (Approved and potential)</th>
<th>Proteinuria (Risk Factors: CKD, HTN, RCC)</th>
<th>Hypertension (Risk factors: age &gt;60, BMI &gt; 25 kg/m², &gt;1 anti-VEGF agent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF-Trap (fusion protein)</td>
<td>Alfibercept</td>
<td>Melanoma, prostate cancer, pancreatic cancer, non-small lung cancer</td>
<td>Incidence of 40-60%</td>
<td>Incidence about 40%</td>
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<tr>
<td>VEGF-A monoclonal antibody</td>
<td>Bevacizumab</td>
<td>Glioblastoma, metastatic colorectal cancer, non-small cell lung cancer, renal cell carcinoma</td>
<td>Incidence of 20-60%</td>
<td>Incidence about 20%</td>
</tr>
<tr>
<td>VEGFR2 monoclonal antibody</td>
<td>Ramucirumab</td>
<td>Metastatic colorectal cancer, breast cancer, non-small lung cancer</td>
<td>Incidence about 10%</td>
<td>Incidence about 42%</td>
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<tr>
<td>Tyrosine Kinase Inhibitors</td>
<td>Axitinib</td>
<td>Renal cell carcinoma, thyroid cancer, hepatocellular cancer, gastrointestinal stromal tumors, pancreatic neuroendocrine tumors, soft tissue sarcomas, refractory chronic myelogenous leukemia, and refractory metastatic colorectal cancer</td>
<td>Incidence about 20%</td>
<td>Incidence about 40%</td>
</tr>
<tr>
<td></td>
<td>Cabozantinib</td>
<td>Incidence about 22%</td>
<td>Incidence about 30-60%</td>
<td>Incidence about 30-60%</td>
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<tr>
<td></td>
<td>Lenvatinib</td>
<td>Incidence about 11%</td>
<td>Incidence about 70%</td>
<td>Incidence about 70%</td>
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<tr>
<td></td>
<td>Nintedanib</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td></td>
<td>Pazopanib</td>
<td>Incidence about 13%</td>
<td>Incidence about 35%</td>
<td>Incidence about 35%</td>
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<tr>
<td></td>
<td>Regorafinib</td>
<td>Incidence about 7%</td>
<td>Incidence about 28%</td>
<td>Incidence about 28%</td>
</tr>
<tr>
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<td>Sorafenib</td>
<td>Incidence about 11%</td>
<td>Incidence about 19%</td>
<td>Incidence about 19%</td>
</tr>
<tr>
<td></td>
<td>Cabozantinib</td>
<td>Incidence about 8%</td>
<td>Incidence about 20%</td>
<td>Incidence about 20%</td>
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<tr>
<td></td>
<td>Vandetanib</td>
<td>Incidence about 10%</td>
<td>Incidence about 30%</td>
<td>Incidence about 30%</td>
</tr>
<tr>
<td></td>
<td>Apatinib</td>
<td>Incidence about 15%</td>
<td>Incidence about 9%</td>
<td>Incidence about 9%</td>
</tr>
</tbody>
</table>

BMI: body mass index; CKD: chronic kidney disease; HTN: hypertension; RCC: renal cell carcinoma VEGF: vascular endothelial growth factor.
Figure legends:

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Figure 1 Mechanism of action of the different VEGF signaling pathway inhibitors agents and the pathophysiologic changes leading to hypertension and proteinuria.

Figure 2 A concept map of clinical and pathological clues to differentiate primary versus malignancy-associated membranous nephropathy.

Figure 3: The glomerular diseases seen with immune checkpoint inhibitors

Figure 4 A flowchart of the spectrum of kidney diseases in monoclonal gammopathies, divided into paraprotein-related and treatment-related kidney diseases.
Figure 1. Mechanism of VEGF signaling pathway inhibitors induced hypertension and proteinuria.

VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; Mab: monoclonal antibody; ROS: reactive oxygen species; PIGF: placental growth factor; TKI: tyrosine kinase inhibitor; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; SVR: systemic vascular resistance; ECF: extracellular fluid.
**Figure 2.** Primary versus malignancy associated membranous nephropathy

**Primary**
- Median age of onset: early 50s
- Cancer screening test according to age
- Pathological clues:
  - LM: uniform thickening of GBM, no proliferation.
  - IF: Diffuse, granular, usually IgG4 subepithelial deposits.
- Antigen associated:
  - PLA2R
  - THSD7A
  - PCDH7
  - SEMA 3B
  - NELL-1

**Malignancy Associated**
- Median age of onset >60s
- Most commonly a diagnosis of cancer (lung, breast, etc) before the diagnosis of MN
- Cancer has been detected up to 12 months of diagnosis of MN
- Pathological clues:
  - LM: Endocapillary hypercellularity.
  - IF: IgG1, IgG2, or IgG3 subepithelial deposits.
  - EM: segmental distribution of immune complexes
- Antigens associated:
  - THSD7A
  - NELL-1
  - PCDH7

**EM:** electron microscopy; **GBM:** glomerular basement membrane; **IF:** immunofluorescence; **Ig:** immunoglobulin; **LM:** light microscopy; **MN:** membranous nephropathy; **PLA2R:** phospholipase A2 receptor; **THSD7A:** thrombospondin type I domain-containing 7A; **PCDH7:** protocadherin 7; **SEMA 3B:** semaphorin-3B; **NELL-1:** neural epidermal growth factor-like 1 protein.
Figure 3. Pathogenesis of acute tubular injury, acute interstitial nephritis and glomerular diseases seen with immune checkpoint inhibitors.

Figure 4. Kidney disease spectrum in monoclonal gammopathies.

Kidney disease in the setting of monoclonal gammopathies

Paraprotein-related
- Tissue deposition of paraprotein
  - Amyloidosis (AL, AH, AHL)
  - MIDD - 'randall type' (diffuse tissue deposition)
    - LCDD, HCDD, L&HCDD
- 'Non-randall type'
  - Organized and nonorganized glomerular deposits

Tubular injury
- Tubular dysfunction
  - Crystal storing tubulopathy (κ→λ)
  - Fanconi syndrome (κ→λ)

Functional injury (no monoclonal deposits)
- C3GN
- TMA

Treatment-related
- Proteosome inhibitors
  - Bortezomib: TMA
  - Carfilzomib: Hemodyanmic, TMA

Conventional chemotherapy
- Displatin: TMA, ATI
- Anthracycline: collapsing FSGS, TMA
- Cyclophosphamide: ATI
- Melphalan: ATI
- mTORi: TMA, ATI, FSGS
- ICPI: AIN, ATI
- BRAFi: AIN, ATI
- Immunomodulators
  - Lenalidomide: AIN, Fanconi syndrome
  - Pomalidomide: Crystal nephropathy, ATI, TLS