

# Onconeurology 2022: An Update

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## Abstract

**Onconeurology 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 oncotherapeutic 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 (oncohypertension), and AKI from multiple forms of cancer therapies have been explored. Significant research has also been conducted in the field of transplant onconeurology. 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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## 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 CKD and hypertension (HTN). This has paved a pathway for a new subspecialty of onconeurology. In this review, we shall *update* our readers on the recent studies and trials in various fields of onconeurology: AKI, electrolyte disorders, oncohypertension, glomerular disease, stem cell transplantation, paraprotein and amyloidosis, and transplant onconeurology.

## AKI Update

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

## Immunotherapy-Associated AKI

Immune checkpoint 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,<sup>1</sup> including ICI-associated AKI. Most kidney immune-related adverse events are due to acute interstitial nephritis (AIN).<sup>2</sup>

A large multicenter retrospective study collected over 400 cases of patients with AKI from immune checkpoint inhibitors.<sup>3</sup> These were compared with controls who received ICIs but did not develop AKI. ICI-AKI occurred at 16 weeks (interquartile range [IQR], 8-32). The use of proton pump inhibitor therapy, underlying low eGFR, and presence of extra renal immune-related adverse events were risk factors. AIN was the most common kidney biopsy finding in 83% of patients. Treatment of ICI-AKI with steroids within 14 days after 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 seven studies with a total of 3767 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.<sup>4</sup> 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.

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Although 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-center and multicenter data suggest that a shorter course of steroids with a quick taper is equivalent to a longer course for the treatment of ICI-induced AIN.<sup>5,6</sup>

The addition of ICIs to standard chemotherapy has improved progression-free and overall survival in patients with metastatic nonsquamous non-small cell lung cancer regardless of programmed death–ligand 1 expression.<sup>7</sup> 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 versus 202 days). The kidney biopsy findings were more suggestive of tubular and interstitial damage than AIN alone.<sup>8</sup> Finally, several studies now confirmed the safe use of ICI in patients with ESRD because they had similar incidence of immune-related adverse events compared with the general population. This is likely due to the main mechanism of ICI clearance, through proteolytic catabolism and receptor-mediated endocytosis.<sup>9–11</sup>

Ideally, a noninvasive 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 and urine retinol-binding protein, in predicting ICI related-AKI.<sup>12</sup> Elevated C-reactive protein with an elevated urine retinol-binding protein/creatinine were helpful in identifying patients with ICI-related AKI. A more recent preprint study showed that soluble interleukin-2 receptor level in peripheral blood was significantly higher in patients with ICI-related nephritis compared with ICI-treated controls and hemodynamic AKI controls.<sup>13</sup> A soluble interleukin-2 receptor cutoff point of 1.75-fold upper limit of normal was highly diagnostic of ICI nephritis (area under the curve [AUC] >96%) compared with 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 with ICI-treated controls. Another emerging biomarker is urine TNF- $\alpha$  as its level was significantly elevated in ICI nephritis compared with other causes of AKI.<sup>14</sup> TNF- $\alpha$  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 and positron emission tomography 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 positron emission tomography-computerized tomography, a diffuse increase in radiotracer uptake throughout the renal cortex and a decrease in radiotracer activity in the renal pelvis can be seen.<sup>15</sup>

### Pseudo-AKI from Novel Molecularly Targeted Agents

Three classes of agents, namely mesenchymal-epithelial transition tyrosine kinase inhibitors, inhibitors of polyadenosine diphosphate ribose polymerase, and the cyclin-dependent kinase 4 and 6 inhibitors have been newly associated with pseudo-AKI (an asymptomatic rise in serum creatinine [SCr]).<sup>16</sup> The underlying mechanisms of pseudo-AKI are associated with inhibition of renal transporters such as organic cation transporter-2, multidrug and toxin extrusion-1, and multidrug and toxin extrusion2-K<sup>17</sup> leading to a reversible increase in SCr.<sup>18–21</sup> However, kidney biopsy-proven cases of acute tubular injury have also been reported with cyclin-dependent kinase 4 and 6 inhibitors recently.<sup>22</sup>

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.<sup>23</sup> 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 B-Raf proto-oncogene (BRAF) inhibitor vemurafenib directly causes renal tubular epithelial cell (RTEC) injury *in vitro*.<sup>24</sup> 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).<sup>25</sup> 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.<sup>26</sup> The authors found a significant reduction in FECH activity and heme levels and mitochondrial dysfunction in vemurafenib-treated RTECs. *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 *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.<sup>27</sup> 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. Coincubation 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

**Table 1. Summarized kidney adverse effects from anticancer therapies**

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

ATP, adenosine 5'-triphosphate; ATI, acute tubular injury; NDI, nephrogenic diabetes insipidus; TMA, thrombotic microangiopathy; HTN, hypertension; BTK, Bruton tyrosine kinase; SIADH, syndrome of inappropriate antidiuretic hormone secretion; VEGF, vascular endothelial growth factor; ATIN, acute tubulointerstitial nephritis; FSGS, focal segmental glomerulosclerosis; BCR-ABL, breakpoint cluster region-tyrosine protein kinase ABL-1 gene; BRAF, proto-oncogene B-Raf; BCL-2, B cell lymphoma 2 gene; TLS, tumor lysis syndrome; ALK, anaplastic lymphoma kinase; CDK4/6, cyclin-dependent kinase 4/6; MATE, multidrug and toxin extrusion; PARP, poly-ADP-ribose polymerase; MET, mesenchymal-epithelial transition; EFGFR, epidermal growth factor receptor; DCT, distal convoluted tubule; mTOR, mammalian target of rapamycin; XPO, export protein exportin 1; CAR-T, chimeric antigen receptor T cells; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; MCD, minimal change disease; PD-1, programmed cell death protein 1; FSGS, focal segmental glomerulosclerosis; PDL-1, programmed death-ligand 1 ERK, extracellular signal-regulated kinase.

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.

### Electrolyte Disorders Update

#### 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.<sup>28</sup> 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 hyperprogression of the disease.<sup>29</sup> Hypocalcemia and hyperphosphatemia may be seen with immune checkpoint inhibitors-induced tumor lysis syndrome (TLS). Chimeric antigen receptor T cell 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.<sup>28,30</sup>

#### TLS

TLS is an oncological emergency. It occurs secondary to anticancer 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 pathomechanism, a recent study postulated a novel pathophysiologic model through which AKI is associated with endothelial dysfunction from high levels of extracellular histones.<sup>31</sup> 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,<sup>32,33</sup> and even immune checkpoint inhibitors. Although, data on such associations are related to case reports and case series.<sup>28,32,33</sup>

#### Hyponatremia

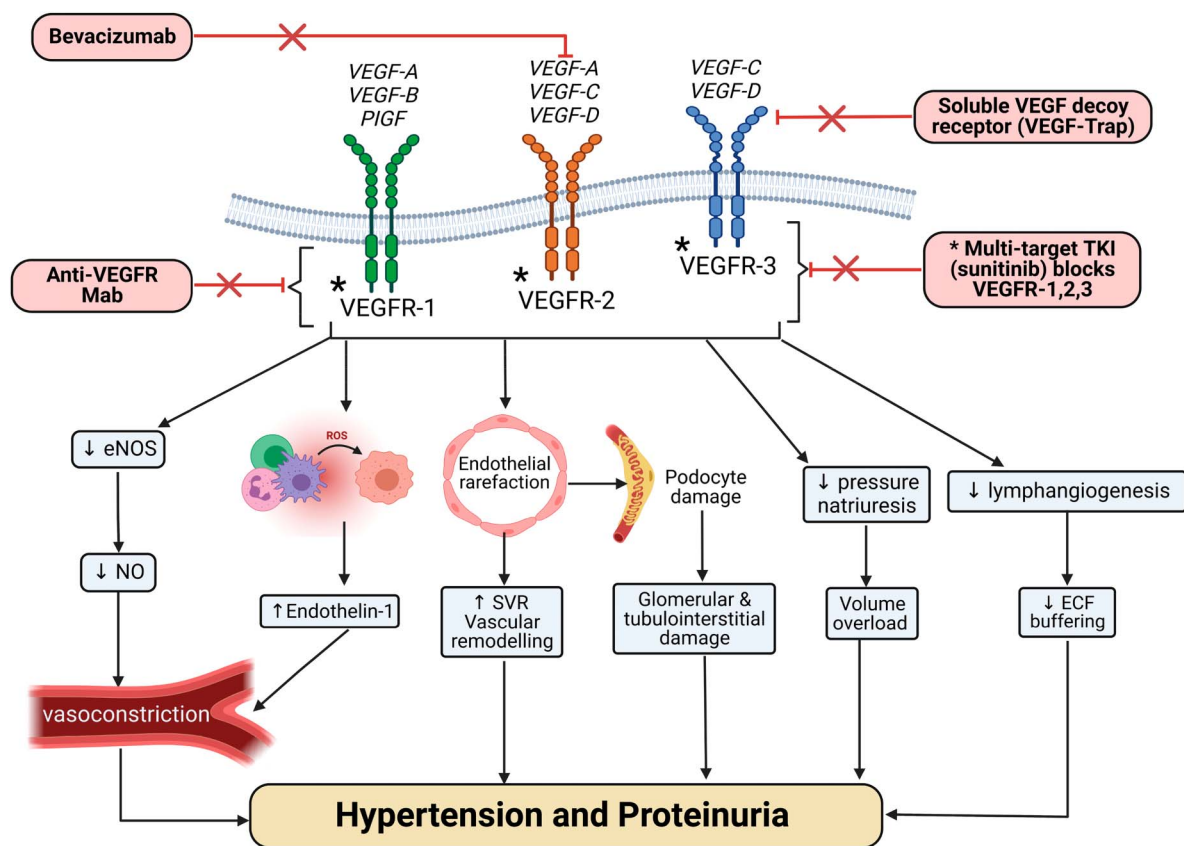
Selinexor is a selective inhibitor of the nuclear export protein exportin 1; it is approved in combination with dexamethasone for the treatment of multiple relapsed or refractory multiple myeloma and for relapsed/refractory diffuse large B cell lymphoma. Selinexor can cause hyponatremia with incidence ranges from 7% to 26%.<sup>34</sup> It is a common grade 3 or 4 adverse event (serum sodium level, <130 mmol/L) in 22% of the patients.<sup>35</sup> 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;

**Table 2. Cancer immunotherapy-associated electrolyte disorders**

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

SIADH, syndrome of inappropriate antidiuretic hormone; CAR-T, chimeric antigen receptor T cells; CRS, cytokine release syndrome; GI, gastrointestinal; RTA, renal tubular acidosis; TLS, tumor lysis syndrome; ICI, immune checkpoint inhibitor; PTHrP, parathyroid-related peptide.





**Figure 1. Mechanism of action of the different VEGF signaling pathway inhibitors agents and the pathophysiologic changes leading to hypertension and proteinuria.** ECF, extracellular fluid; eNOS, endothelial nitric oxide synthase; Mab, monoclonal antibody; NO, nitric oxide; PlGF, placental growth factor; ROS, reactive oxygen species; SVR, systemic vascular resistance; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

nausea and volume depletion, and possible unidentified kidney factor.<sup>36</sup>

Immune checkpoint inhibitors and chimeric antigen receptor T cell therapy have also been associated with hyponatremia (Table 2).<sup>37</sup> While initially believed to be related to endocrinopathies, syndrome of inappropriate antidiuresis is the most common mechanism for hyponatremia.<sup>38,39</sup>

### Magnesium Disorders in Patients with Cancer

Hypomagnesemia is another crucial electrolyte disorder in patients with cancer, 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 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.<sup>40</sup> Cetuximab-induced hypomagnesemia is also secondary to primary renal magnesium wasting, mechanistically from an inhibition of the basolateral epidermal growth factor receptor, which prevents the transcellular magnesium reabsorption through the transient receptor potential cation channel

subfamily M member 6 (TRPM6) Mg channels.<sup>41</sup> Sodium glucose transporter 2 inhibitors have been used in patients with refractory hypomagnesemia above and beyond the magnesium replenishment.<sup>42,43</sup> A meta-analysis showed increased serum Mg levels in patients by 0.15–0.24 mg/dl, but the exact mechanism of this effect is unknown.<sup>44</sup> A plausible explanation of improvement in Mg<sup>2+</sup> levels is by increased Mg<sup>2+</sup> absorption in the intestine or reabsorption in the kidney, possibly by enhancing TRPM6-mediated transport in the intestine and/or the kidney.<sup>45</sup>

### Oncohypertension Update

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

### VEGF Signaling Pathway Inhibitors–Induced HTN

VEGF signaling pathway inhibitors are the prototype of anticancer drug-induced HTN (Figure 1), observed in

**Table 3. Anti-VEGF signaling pathway agents kidney adverse events<sup>49,53–57</sup>**

Anti-VEGF Agents Subclasses	Drugs	Indications (Approved and Potential)	Proteinuria (Risk Factors: CKD, HTN, RCC)	Hypertension (Risk Factors: Older Than 60 Years, BMI>25 kg/m <sup>2</sup> , >1 Anti-VEGF Agent)
VEGF-Trap (fusion protein)	Alficercept	Melanoma, prostate cancer, pancreatic cancer, non-small lung cancer	Incidence of 40%–60%	Incidence about 40%
VEGF-A monoclonal antibody	Bevacizumab	Glioblastoma, metastatic colorectal cancer, NSCLC, renal cell carcinoma	Incidence of 20%–60%	Incidence about 20%
VEGFR2 monoclonal antibody	Ramucirumab	Metastatic colorectal cancer, breast cancer, non-small lung cancer	Incidence about 10%	Incidence about 42%
Tyrosine kinase inhibitors	Axitinib	Renal cell carcinoma,	Incidence about 20%	Incidence about 40%
	Cabozantinib	thyroid cancer,	Incidence about 22%	Incidence about 30%–60%
	Lenvatinib	hepatocellular cancer,	Incidence about 11%	Incidence about 70%
	Nintedanib	gastrointestinal stromal	n/a	n/a
	Pazopanib	tumors, pancreatic	Incidence about 13%	Incidence about 35%
	Regorafenib	neuroendocrine tumors,	Incidence about 7%	Incidence about 28%
	Sorafenib	soft tissue sarcomas,	Incidence about 11%	Incidence about 19%
	Cabozantinib	refractory chronic	Incidence about 8%	Incidence about 20%
Vandetanib	myelogenous leukemia,	Incidence about 10%	Incidence about 30%	
Apatinib	and refractory metastatic colorectal cancer	Incidence about 15%	Incidence about 9%	

VEGF, vascular endothelial growth factor; HTN, hypertension; RCC, renal cell carcinoma; BMI, body mass index; NSCLC, non-small cell lung cancer; VEGFR, vascular endothelial growth factor receptor; n/a, none available.

20%–90% depending on VEGF signaling pathway inhibitors (VEGFi) type and BP definitions.<sup>49,50</sup> Risk factors for the development of HTN include a previous history of HTN, ages 60 years or older, body mass index  $\geq 25$  kg/m<sup>2</sup>, concurrent use of more than one VEGFi medication, as well as tumor type such as renal cell carcinoma.<sup>49,51</sup> Not much has been reported on the management of VEGFi-induced HTN in the last few years. A recent review summarizes these findings.<sup>52</sup> Table 3 summarizes anti-VEGF signaling pathway agents kidney adverse events.<sup>49,53–57</sup> The mechanism of VEGFi-induced HTN is shown in Figure 1.

#### Bruton 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.<sup>58,59</sup> In this systematic review with meta-analysis of randomized controlled trials, the relative risk of HTN with ibrutinib therapy was 2.82 (95% confidence interval [CI], 1.52 to 5.23),<sup>58,60</sup> with a range of HTN incidence from 18% to 75%.<sup>58,61</sup> 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 downregulation have been postulated.<sup>50</sup> So far, data indicate a lower incidence of HTN with second-generation BTK inhibitors such as acalabrutinib.<sup>50,62</sup>

#### Phosphatidylinositol-3 Kinase Inhibitors–Induced HTN

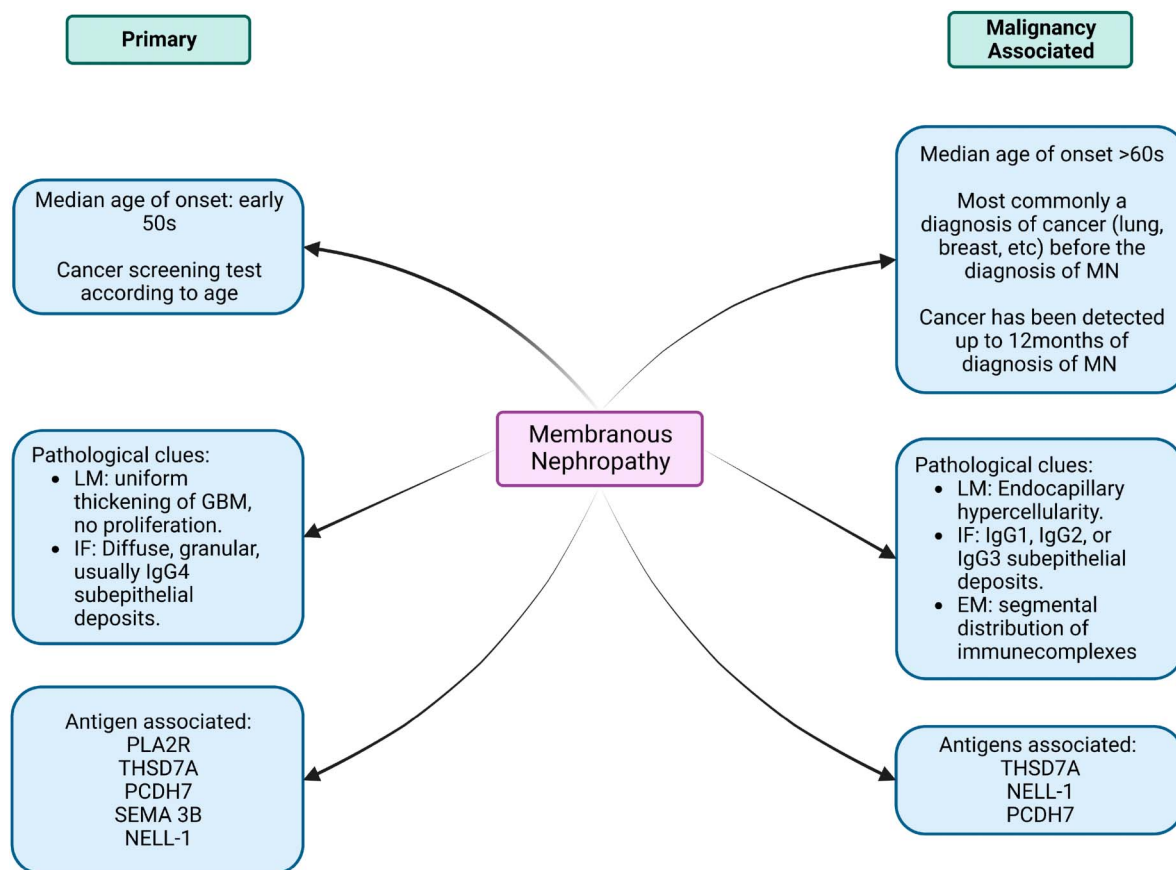
Toxicities from small-molecule phosphatidylinositol-3 kinase (PI3K) inhibitors depend on their PI3K isozyme specificity. Copanlisib is a pan-PI3K with nonselective blockage of PI3K signaling approved for the third-line treatment of follicular non-Hodgkin lymphoma.<sup>63</sup> HTN occurs primarily during infusion in almost 30% of the patients, and it is transient, resolving within 24 hours, and usually less prominent with subsequent cycles.<sup>63,64</sup> The mechanism is likely related to targeting the PI3K- $\alpha$  isoform.<sup>65</sup> PI3K- $\alpha$  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.<sup>66</sup> Idelalisib and duvelisib target the PI3Kp110 $\delta$  isoform and are also known to induce HTN.<sup>66,67</sup>

#### 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.<sup>68</sup>

#### Other Miscellaneous Anticancer Agents Associated with HTN

BRAF/mitogen-activated protein kinase kinase (MEK) inhibitors are used in the treatment of BRAF-mutant melanoma and colorectal cancer, with HTN being the most common



**Figure 2.** A concept map of clinical and pathological clues to differentiate primary versus malignancy-associated membranous nephropathy. EM, electron microscopy; GBM, glomerular basement membrane; IF, immunofluorescence; LM, light microscopy; MN, membranous nephropathy; NELL-1, neural epidermal growth factor–like 1 protein; PCDH7, protocadherin 7; PLA2R, phospholipase A2 receptor; SEMA 3B, semaphorin-3B; THSD7A, thrombospondin type 1 domain–containing 7A.

cardiovascular adverse event reported with these drugs.<sup>69</sup> HTN occurs in approximately 14% and 20% of patients treated with BRAF inhibitor monotherapy and BRAF/MEK inhibitors, respectively.<sup>69</sup> The mechanism may be related to decrease of nitric oxide bioavailability, causing vasoconstriction and, consequently, HTN.<sup>69</sup> Polyadenosine diphosphate ribose polymerase inhibitors have been used to treat ovarian cancer, and HTN has developed in 12%–20% versus 1%–6% of placebo.<sup>70,71</sup> However, the mechanism leading to HTN is not entirely understood. The antiandrogens, abiraterone, and enzalutamide, used for prostate cancer, have been associated with the development of all-grade HTN in 26% and 11%, respectively.<sup>72</sup> Abiraterone inhibits cytochrome P450 enzymes leading to the accumulation of mineralocorticoid precursors and contributing to its prohypertensive effects.<sup>72</sup> However, the mechanisms underlying enzalutamide-induced HTN remain unclear. Aromatase inhibitors such as anastrozole used for estrogen-positive breast cancer have been associated with higher rates of HTN and cardiovascular events.<sup>73</sup>

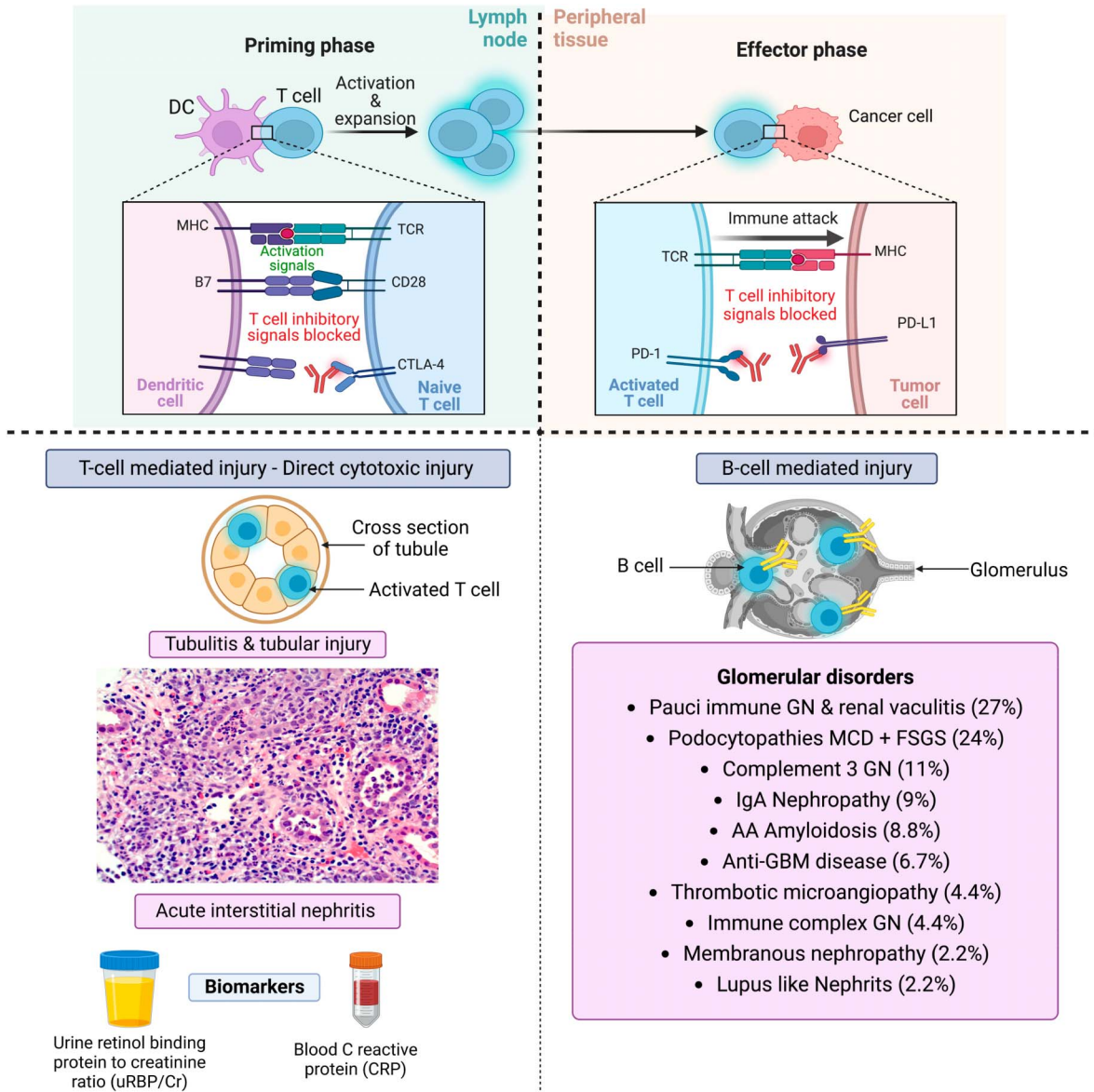
### Glomerular Diseases and Cancer Update

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%–3% of MN cases in western countries.<sup>74</sup> It is also overexpressed in certain malignancies such as gall bladder and endometrial cancers.<sup>75</sup> Strong THSD7A staining has also been seen in prostate, breast, kidney, and colorectal cancers.<sup>76</sup> 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 phospholipase A2 receptor (PLA2R)–negative MN cases without any identifiable secondary cause.<sup>77</sup> The current literature suggests a connection between NELL-1-associated MN and malignancy.<sup>78</sup> In addition, 21.4% of patients with protocadherin 7-associated MN had a malignancy.<sup>79</sup> 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



**Figure 3. The glomerular diseases seen with immune checkpoint inhibitors.** CTLA-4, cytotoxic T lymphocyte-associated protein-4; DC, dendritic cell; MCD, minimal change disease; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein-associated ligand-1; TCR, T cell receptor.

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 GN and renal vasculitis (27%), podocytopathies (24%), and complement 3 GN (C3GN; 11%).<sup>80</sup> Since then, several other glomerular pathologies have been reported and observed (unpublished) in clinical practice such as MN, mesangioproliferative GN, and other podocytopathies (Figure 3).<sup>80–83</sup> Treatment of glomerular diseases associated with ICI is challenging.

### Hematopoietic Stem Cell Transplantation–Related Renal Disease Update

Renal disease after hematopoietic stem cell transplantation (HSCT) includes AKI and CKD, both of which result in high morbidity and mortality.<sup>84</sup> Below are two novel

concepts noted in the literature on renal 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 AKI. The high incidence of CRS seen in haploidentical peripheral blood transplants compared with bone marrow



transplants is due to the presence of eight-fold more lymphocytes in peripheral blood allografts.<sup>85</sup>

In a small retrospective study spanning 13 years of a total of 55 cases of confirmed haplostorm, seven were found to have haplostorm associated with AKI (13%). All these patients suffered from severe CRS characterized by hypotension with pressor support requirement and hypoxemia requiring supplemental oxygen.<sup>86</sup> In another study by Imus *et al.*<sup>87</sup> 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.<sup>88</sup> 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,<sup>89,90</sup> most cases are PLA2R-negative, and the target antigen remains unknown. Recently, Nasr *et al.*<sup>91</sup> reported five patients with MN and extensive tubular basement membrane deposits after 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, and SEMA3B. Only one of five patients tested positive for PLA2R, while the identity of the target antigen in the remaining cases remained unknown. NELL-1-associated membranous GN after HSCT has also been described.<sup>92</sup> A study published by Sethi *et al.*<sup>93</sup> revealed a novel protein, protocadherin (FAT1), which was detected by microdissection and mass spectrometry in patients with HSCT-associated MN, 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.<sup>94</sup> 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.<sup>95</sup> The authors postulate that a somatic/previously hidden FAT1 mutation may cause an immune response as a consequence of graft versus host disease in most of these cases.<sup>93,96</sup>

### Paraproteinemia and Amyloidosis Update Multiple Myeloma and Other Forms of Monoclonal Gammopathy of Renal Significance

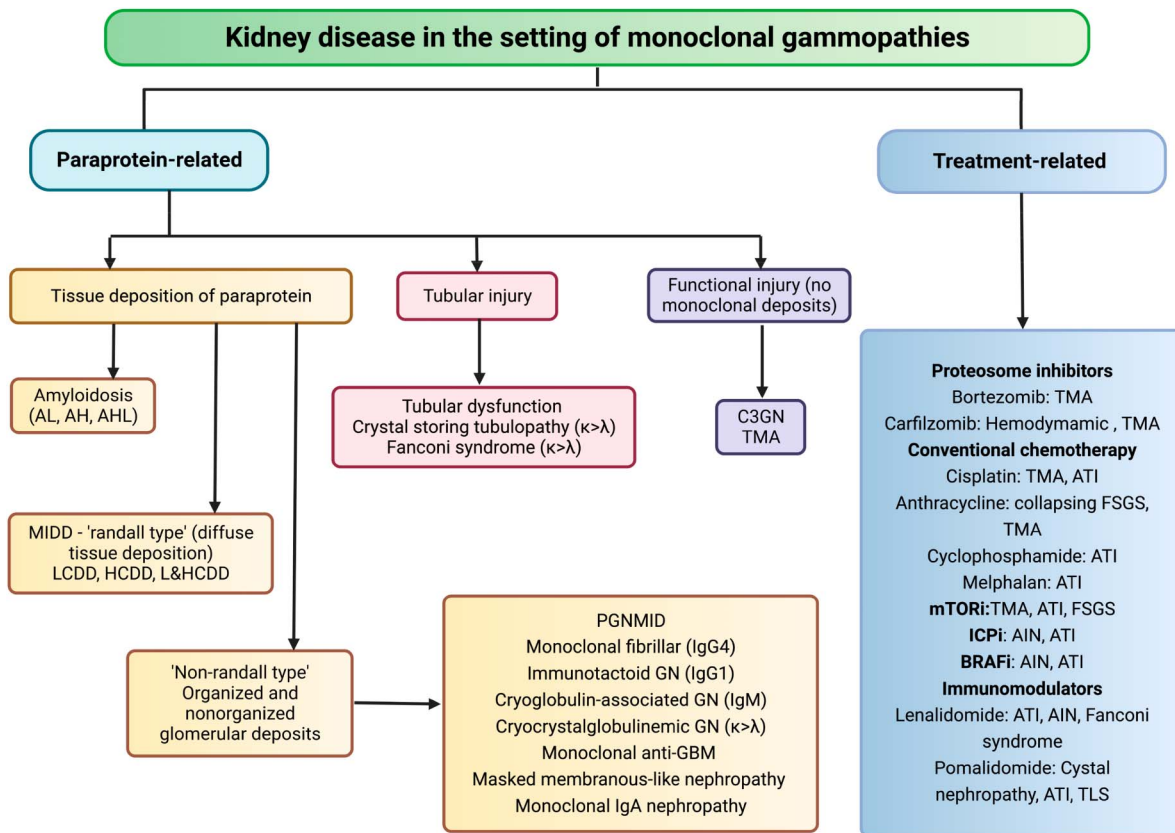
The new International Kidney and Monoclonal Gammopathy Research Group consensus definition of monoclonal gammopathy of renal significance (MGRS) includes all B cell or plasma cell proliferative disorders that produce a nephrotoxic monoclonal immunoglobulin. A recent study demonstrated that 98% of patients with cast nephropathy (CN) diagnosis presented with serum-free light chains (sFLC) levels >500 mg/L.<sup>97</sup> As per the International Myeloma Working Group, CN was characterized by the

presence of histopathological features or the involved sFLC of more than 1500 mg/L.<sup>98</sup> A recently published retrospective French study outlined a distinct subset of patients with MGRS who develop thrombotic microangiopathy. Prognostically, this is an important phenotype, with 70% of patients needing dialysis at the disease onset and median renal survival being 20 months.<sup>99</sup> A Chinese single-center large cohort study<sup>100</sup> 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%—thrombotic microangiopathy). 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<sup>101</sup> compared double (bortezomib+dexamethasone [BD]) versus triple (cyclophosphamide+bortezomib+dexamethasone [C-BD]) regimens in patients with multiple myeloma (MM) and AKI from CN. The study did not show any benefit of C-BD compared with 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 (Figure 4). 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 (Figure 4). In a setting of plasma cell clones, the best results are achieved using proteasome inhibitor-based regimens.<sup>102,103</sup> Other therapies are melphalan followed by autologous HSCT in patients with monoclonal Ig deposition disease,<sup>104</sup> anti-CD-38 monoclonal antibody, daratumumab for proliferative GN with monoclonal deposits,<sup>105</sup> and rituximab-based therapy for patients with B cell clone which express CD-20.<sup>102</sup> Daratumumab may become standard therapy for several diseases with the MGRS phenotype based on its recent success in a pilot study for proliferative GN with monoclonal deposits.<sup>105</sup>

Therapies available for amyloid light chain (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).<sup>106</sup> In a recent randomized controlled trial with newly diagnosed AL amyloidosis, the addition of daratumumab to CyBorD was associated with higher frequencies of hematological complete response and survival.<sup>107</sup>

Extracorporeal therapies used for the removal of sFLC are plasma exchange (PLEX) and high cutoff (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 1.73 m<sup>2</sup> at 6 months.<sup>108</sup> Multiple myeloma and renal failure due to myeloma cast nephropathy<sup>109</sup> and the European Trial of Free Light Chain Removal by Extended Hemodialysis in Cast Nephropathy<sup>109,110</sup> used 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



**Figure 4. A flowchart of the spectrum of renal diseases in monoclonal gammopathies, divided into paraprotein-related and treatment-related renal diseases.** AH, amyloid heavy chain; AHL, amyloid light and heavy chain; AIN, acute interstitial nephritis; AL, amyloid light chain; ATI, acute tubular injury; BRAFi, v-raf murine sarcoma viral oncogene homolog B1 inhibitor; C3, complement 3; HCDD, heavy chain deposition disease; ICPi, immune checkpoint inhibitor; IgG 1&4, immunoglobulin G type 1&4; IgM, immunoglobulin M; LCDD, light chain deposition disease; LHCD, light-heavy chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease; mTORi, mammalian target of rapamycin inhibitor; PGMIDD, proliferative N with monoclonal IgG deposits; TMA, thrombotic microangiopathy; TLS, tumor lysis syndrome.

burden to improve kidney outcomes remains elusive and cannot be routinely recommended.

### Transplant Onconeurology Update

The field of transplant onconeurology has now been increasingly recognized.<sup>111</sup> Recent advancements in cancer treatment have changed the landscape of pretransplant 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.<sup>112</sup> 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 mammalian target of rapamycin 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.<sup>113</sup> 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 mammalian target of rapamycin 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.<sup>114</sup> However, acute rejection can still occur in patients on KRT 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.<sup>9</sup>

### Can a Patient with Myeloma and Light/Heavy Chain Amyloidosis Get a Kidney Transplant?

Patients with ESRD 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.<sup>9,115</sup> Data on outcomes of patients with MM and amyloidosis-induced ESRD getting a kidney transplant were limited to case reports and case series.<sup>116</sup> A recent retrospective study of the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) dataset (2006–2018) compared patient and graft outcomes of kidney transplant recipients with ESRD due to plasma cell dyscrasias (PCD) versus other causes.<sup>117</sup> Among 168,369 first kidney transplants adult recipients, 0.22%–0.43% per year (a very small proportion) had PCD as the cause of ESRD. The PCD group had worse survival than the non-PCD group for both living and deceased donor types (adjusted hazard ratio [aHR], 2.24; 95% CI, 1.67 to 2.99 and 1.40; 95% CI, 1.08 to 1.8). The PCD group had worse survival than the diabetes group but only among living donor types (aHR, 1.87; 95% CI, 1.37 to 2.53 versus 1.16; 95% CI, 0.89 to 1.2). Graft survival in patients with the PCD was worse than non-PCD in both living and deceased donor types (aHR, 1.72; 95% CI, 1.91 to 2.56 versus 1.30; 95% CI, 1.03 to 1.66). Patient and graft survival were worse in amyloidosis but not statistically different in multiple myeloma, compared with the non-PCD group. The comparison of outcomes of patients with ESRD due to PCD in the context of other causes of ESRD 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.<sup>118</sup> 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 with less than VGPR (9 versus 6.8 years; HR, 1.5; 95% CI, 1 to 2.1;  $P=0.04$ ) at renal transplantation. Median graft survival was 7.8 years and was better in the CR+VGPR group (8.3 versus 5.7 years, HR, 1.4; 95% CI, 1 to 2;  $P=0.05$ ). The frequency and time to amyloid recurrence in the graft were also lower (16% versus 37%,  $P=0.01$ ) and longer (median time not achieved versus 10 years,  $P=0.001$ ) in the CR+VGPR group. Comparing CR versus 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 patients with AL amyloidosis 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.

Since the inception of the field of onconeurology 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 onconeurology has seen recent advancements in

the treatment of patients on immunotherapy and how to navigate the challenges of a patient with paraproteinemia and ESRD now needing a kidney transplant. The field of onconeurology is currently ripe for more ongoing original investigations.

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#### Author Contributions

M. Bonilla conceptualized the study, was responsible for formal analysis, and provided supervision; K.D. Jhaveri was responsible for data curation; M. Bonilla and K.D. Jhaveri were responsible for validation and visualization; M. Bonilla, P. Gudsoorkar, and K. Jhaveri wrote the original draft; and M. Bonilla, P. Gudsoorkar, S.M. Herrmann, K.D. Jhaveri, and R. Wanchoo reviewed and edited the manuscript.

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