Onconephrology: The Intersections Between the Kidney and Cancer

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Abstract: Onconephrology is a new subspecialty of nephrology that recognizes the important intersections of kidney disease with cancer. This intersection takes many forms and includes drug-induced nephrotoxicity, electrolyte disorders, paraneoplastic glomerulonephritis, and the interactions of chronic kidney disease with cancer. Data clearly demonstrate that, when patients with cancer develop acute or chronic kidney disease, outcomes are inferior, and the promise of curative therapeutic regimens is lessened. This highlights the imperative for collaborative care between oncologists and nephrologists in recognizing and treating kidney disease in patients with cancer. In response to this need, specific training programs in onconephrology as well as dedicated onconephrology clinics have appeared. This comprehensive review covers many of the critical topics in onconephrology, with a focus on acute kidney injury, chronic kidney disease, drug-induced nephrotoxicity, kidney disease in stem cell transplantation, and electrolyte disorders in patients with cancer.

Epidemiology of Kidney Disease in the Patient With Cancer

Patients with cancer may develop AKI or may have preexisting CKD (defined as abnormalities of kidney function or structure present for more than 3 months) that impacts their care.
Chronic Kidney Disease in Patients With Cancer

CKD may preexist in a substantial number of patients with cancer. This is likely because of comorbid conditions, such as diabetes mellitus and hypertension, that are highly prevalent in the population. In addition, as described below, CKD in itself may be associated with a higher risk for certain malignancies, especially those of the urinary tract. Two observational studies demonstrated that nearly 50% of patients with cancer had an estimated glomerular filtration rate (eGFR) < 90 mL/minute/1.73 m².1,2 Much of the CKD in this population was modest in degree, as the prevalence of stage 3 (eGFR, 30-59 mL/minute) CKD was 12%, and < 1% of patients had stage 4 (eGFR, 15-29 mL/minute) CKD.1,2 In another study of 4077 patients with cancer, 30% had an eGFR of < 60 mL/minute/1.73 m², and 8.3% had an eGFR of 45 mL/minute/1.73 m², signifying that a substantial proportion of the cancer population had clinically significant CKD that might affect care (such as drug dosing).3 Other studies have shown an even higher prevalence of CKD; for instance, only 38.6% of patients with breast cancer, 38.9% of patients with lung cancer, 38.3% of patients with prostate cancer, 27.5% of patients with gynecologic cancer, and 27.2% of patients with colorectal cancer had a glomerular filtration rate (GFR) ≥ 90 mL/minute/1.73 m² at the time of therapy initiation in several studies.4,5 Overall, as shown in Figure 1, CKD (defined as an eGFR < 60 mL/minute/1.73 m²) prevalence ranges from 12% to 25% across many cancer populations.1-12 Because cancer has a greater incidence in individuals aged > 65 years, it is not known whether the association with mild degrees of CKD (eGFR, 45-60 mL/minute) may simply reflect age-related decreases in GFR versus true intrinsic kidney disease. This is an ongoing debate in the field of nephrology, and current recommendations argue that a universal eGFR threshold of 60 mL/minute/1.73 m² should be used as the definition of CKD. This threshold has been defended by epidemiological studies showing that the risk of mortality or end-stage renal disease increases with an eGFR < 60 mL/minute/1.73 m². However, a universal threshold does not take into account the physiologic decline in GFR with ageing, nor does it account for the risk of mortality and end-stage kidney disease (ESKD) being trivial with isolated eGFR levels just below 60 mL/minute/1.73 m² in the elderly. An age-calibrated definition of CKD has been proposed to distinguish age-related from disease-related changes in eGFR, and individuals with an eGFR < 45 mL/minute/1.73 m² almost certainly have significant CKD independent of age-related decreases in GFR.

CKD in patients who have cancer is associated with reduced survival. Several studies have demonstrated that stage 3 or 4 CKD is associated with an approximately 12% to 27% higher risk for death compared with patients who have cancer with preserved GFR.4-6 As an example, in a cohort of 8223 patients who had cancer, cancer-specific mortality had an adjusted hazard ratio (aHR) of 1.12 for those with an eGFR of 30 to 59 mL/minute/1.73 m² (95% CI, 1.01-1.26; P = .04) and an aHR of 1.75 for those with an eGFR < 30 mL/minute/1.73 m² (95% CI, 1.32-2.32; P < .001). The reasons for the higher mortality rate with CKD remain uncertain, but speculation is that CKD limits options for chemotherapy and access to clinical trials. In addition, dosing of several chemotherapeutic agents is changed in CKD, and this may lower efficacy and increase the risk of side effects. Other comorbidities associated with CKD, such as diabetes mellitus, hypertension, and heart failure, also have a role in the excess mortality seen in this group. Further study of this issue is needed.

Acute Kidney Injury in Patients With Cancer

AKI, as defined by the Kidney Disease Improving Global Outcomes (KDIGO) or other AKI grading systems (Fig. 2), is a common occurrence in patients with cancer.7-9,13-15 For instance, in a study from Denmark of 1.2 million people, there were 37,267 patients with incident cancer between 1999 and 2006. Over a 5-year period, 27% of patients developed AKI (defined as an increase > 50% in serum creatinine), and 7.6% of patients developed severe
AKI and AKI requiring dialysis support. In that study, the highest risk of AKI was among patients with kidney and liver cancer and MM. In a more recent study of 163,071 patients undergoing therapy for cancer between 2007 and 2014, AKI that required dialysis occurred in nearly 10% of all patients (the highest incidence was reported in patients with MM, bladder and kidney cancer, and acute leukemia). Advanced cancer stage, CKD, and diabetes were associated with an increased risk of AKI. The annual incidence of AKI increased from 18 to 52 cases per 1000 person-years over the duration of the study period. This rise in AKI was likely explained in part by an increase in drug-related kidney toxicities.

A study in France investigated the outcomes of patients who were admitted to the intensive care unit (ICU) with a solid organ malignancy. In this patient cohort, KDIGO stage 3 AKI occurred in 28% of patients, and 42% of those patients died. The overall AKI rate (including all stages) was 59%, and the mortality rate at 90 days was 37%. The most common etiologies of AKI in this ICU cohort were sepsis, hypovolemia, urinary tract obstruction, tumor lysis syndrome (TLS), and hypercalcemia. In several studies, the development of AKI in patients with cancer negatively affected short-term and long-term mortality. Importantly, patients with AKI who required dialysis had particularly poor outcomes, as described in a study from a Brazilian ICU in which these patients had a hospital mortality rate of 87% compared with 14% for patients with no AKI.

Assessment of Kidney Function in Patients With Cancer

Accurate dosing of chemotherapeutic agents is required to ensure optimal outcomes and to avoid toxicity. For those drugs excreted through the kidney, a determination of an individual’s kidney function is required. For drug dosing, the best measure of kidney function is the GFR. For drugs like capecitabine, etoposide, carboplatin, cisplatin, mitomycin, methotrexate, pemetrexed, pentostatin, topotecan, and bleomycin, which are largely excreted by the kidney, this knowledge is critical. In fact, carboplatin is unique among chemotherapeutic agents, in that its dosing is largely based on determination of the eGFR. Highlighting the prevalence of this issue were the Renal Insufficiency and Anticancer Medications (Insuffisance Renale et Medicaments Anticancereux [IRMA]) studies, in which 79.9% of patients received at least one drug that required dose modification for kidney function, and 80.1% of patients received at least one anticancer drug with significant nephrotoxicity risk potential.

Current methodologies for the measurement of kidney function have limitations in the patient with cancer because of their reliance on serum creatinine. Serum creatinine is influenced by poor dietary intake of protein, muscle wasting, malnutrition, changes in hydration, and liver disease; all common in patients with cancer. A recent study demonstrated the problems in using serum creatinine for determination of the GFR. In that study, an abnormal serum creatinine result was seen in <10% of patients with cancer; however, an abnormal GFR was seen in approximately 50% of patients. The impact of the failure to recognize impaired kidney function has clinical significance. In a study of patients with metastatic colon cancer who received a combination of capecitabine and oxaliplatin, patients were dosed based on their serum creatinine values, which were in the normal range. Patients were stratified based on creatinine clearance, as determined by the Cockcroft-Gault formula (creatinine clearance = [(140 – age in years) x (weight in kg)]/[(72 x serum creatinine in mg/dL; multiply by 0.85 for women)]. In doing so, 35% of patients with a creatinine clearance <60 mL/minute (despite normal serum creatinine values) were identified. Drug toxicity, including cytopenias, stomatitis, diarrhea, and hand-foot syndrome, were much more common in the group with unidentified kidney disease. An example in which accurate assessment of GFR and targeted dosing led to better outcomes was a trial of cyclophosphamide and doxorubicin or cyclophosphamide, methotrexate, and fluorouracil over capecitabine in women with early stage breast cancer. The measurement of kidney function with the Cockcroft-Gault formula and subsequent dosing alterations

| Stage | Serum Creatinine Criteria | Urine Output Criteria |
|-------|--------------------------|-----------------------|
| 1     | Creatinine 1.5 to 1.9 times baseline within 7 days, OR Creatinine increase > 0.3 mg/dL within 48 hrs | < 0.5 ml/kg/hr x 6-12 hours |
| 2     | Creatinine 2.0-2.9 times baseline | < 0.5 ml/kg/hr for > 12 hours |
| 3     | Creatinine > 3 times baseline, OR Creatinine > 4 mg/dL, OR Initiation of dialysis | < 0.3 ml/kg/hr for > 24 hours, OR anuria > 12 hours |

FIGURE 2. The Kidney Disease Improving Global Outcomes (KDIGO) Staging and Definition System for Acute Kidney Injury. Anuria is defined as <50 mL/day (see Kemlin et al, 2018; Benoit & Hoste, 2010; and Liborio et al, 2011).
led to equivalent outcomes and similar rates of complications in the groups with and without kidney disease.21

### Serum Creatinine and the Measurement of Kidney Function

Serum creatinine levels only roughly track with the GFR because of factors such as age, muscle mass, meat intake, and race. Further compounding the accuracy of using creatinine for GFR measurements is that creatinine production is influenced by variables such as age, sex, nutritional status, muscle mass, and intake of creatine supplements.22 In addition, a significant proportion (range, 10%-40%) of creatinine excretion in the urine is because of proximal tubular secretion, which can lead to erroneous overestimation of the GFR if only the serum creatinine is used. Thus clinically significant falls in GFR that may affect drug clearance may not be detectable by rises in serum creatinine. Therefore, either GFR estimation equations (which adjust for some of these confounding factors) or measured creatinine clearance must be used to better assess GFR. In fact, one study showed that, among patients with cancer who had normal serum creatinine measurements, 1 of 5 patients had asymptomatic kidney insufficiency, as assessed by a standard creatinine clearance method.23 Finally, serum creatinine is an insensitive indicator of kidney function, as patients can lose significant amounts of GFR without changes in creatinine values, and the changes in serum creatinine can lag from 24 to 72 hours after a kidney insult.23

Cystatin C is a 13,000-Dalton cysteine proteinase inhibitor produced by all nucleated cells at a constant rate. It is freely filtered at the glomerulus and then undergoes catabolism within the kidney tubules, resulting in insignificant urinary excretion. Thus the serum level of cystatin C depends on the GFR, and it can be used as a measure of kidney function.24 Within oncology, the use of isolated cystatin C measurements for the determination of GFR and detection of nephrotoxicity has been questioned, as there appear to be independent effects of both the malignancy and chemotherapy on cystatin C levels that confound its utility.25,26

### Estimation of GFR Through Regression Equations

Current estimation of GFR is typically through various regression equations, which may include: creatinine clearance estimation, eGFR measurements, or cancer-specific equations. Although the National Comprehensive Cancer Network and the International Society of Geriatric Oncology recommend an assessment of kidney function before the administration chemotherapeutic drugs, even in patients with normal kidney function, there are no guidelines declaring which method of estimating kidney function is preferred in patients with cancer. Given their ease of use and extensive validation studies, regression equations (eGFR measurements, creatinine clearance estimations, and cancer-specific equations) are most commonly used. These GFR-estimating equations use endogenous filtration markers such as serum creatinine and serum cystatin C.27

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is currently recommended by the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative and the Kidney Disease Improving Global Outcomes guideline groups.28 This equation uses the variable of race (Black or other), age, sex, and serum cystatin C. The CKD-EPI equation has been validated in cohort studies of patients with cancer.29 Over the past few years, several publications have shown superior performance of the CKD-EPI equation in the cancer population over other methodologies.30,31 Although GFR-estimating equations have been developed specifically for the cancer population, there is no evidence that these equations are superior to the standard and more widely accepted CKD-EPI equation.29,32

One exception is the use of a dose-determining formula based on GFR (Calvert formula). This formula uses a drug target area under the curve (AUC) as well as the GFR to calculate a drug dose. This approach has been well documented for carboplatin dosing, especially in patients with ovarian and seminoma cancer, in whom a target AUC of 4 to 6 mg/mL/minute was determined to be the most appropriate therapeutic range.33 The National Comprehensive Cancer Network recommends using the Calvert calculation for carboplatin dosing based on specific AUC targets (such as 4-6 mg/mL/minute).

### Acute Kidney Injury

As described above, AKI is a common occurrence in patients with cancer. The diagnostic schema for AKI in the patient with cancer is the same as that for other patient groups and rests on determining whether the etiology is prerenal (from volume depletion or decreased effective circulating volume), intrarenal (such as from vascular, glomerular, tubular, or interstitial causes or postrenal [because of obstruction of urine flow at some point along the urinary tract]). Prerenal etiologies are especially common and are depicted in Figure 3. It is important to recognize prerenal etiologies because these can often be reversed. These etiologies are diagnosed through a review of medical records documenting fluid balances, past medical history, and medication history and a physical examination looking for signs of volume depletion and poor perfusion. Laboratory testing showing an elevated blood urea nitrogen-to-serum creatinine ratio, a fractional urine sodium excretion rate <1% in oliguric patients, and the absence of urinary granular casts can be confirmatory, but
the diagnostic sensitivity and specificity of any one clinical or laboratory finding can be low, thus a multimodal (history, physical examination, imaging, and laboratory testing) approach is needed. In unclear cases, a trial of intravenous fluids (either crystalloids or colloids) in patients with suspected volume depletion should be attempted to determine whether the patient responds with an improvement in GFR and urine output.

**Tumor Lysis Syndrome**

TLS is an emergency in which breakdown of tumor cells, either spontaneously or in response to treatment, releases intracellular contents into the circulation, resulting in hyperuricemia, hyperkalemia, hyperphosphatemia, secondary hypocalcemia, metabolic acidosis, and AKI. The in-hospital mortality rate associated with TLS can be as high as 20%, and nearly 70% of patients experience serious complications such as sepsis, need for acute dialysis, acute respiratory failure, need for mechanical ventilation, cardiac arrest, or seizures. There are important caveats with these criteria because patients with TLS may not have laboratory manifestations present at the same time, and the changes in laboratory values may or may not be significant and can be confusing to apply in clinical situations.

The current definition of TLS is also not sensitive or specific for the occurrence of spontaneous TLS.

The pathophysiology of TLS is because of tumor cell lysis with the release of intracellular constituents, such as potassium and phosphate. The release of deoxyribonucleic acid (DNA) leads to an increase in purines (adenosine and guanosine), which are converted to uric acid through the actions of xanthine oxidase (Fig. 4). The release of large amounts of phosphate increases the calcium-phosphate concentration product, leading to calcium-phosphate precipitation with nephrocalcinosis and hypocalcemia. The mechanisms of AKI are at least partially because of elevated uric acid levels (uric acid nephropathy) but likely also involve cytokine release and nephrocalcinosis. Uric acid nephropathy in patients with TLS is the result of filtration
of high levels of intratubular uric acid, leading to precipitation once the concentration exceeds its solubility. The precipitation of uric acid leads to intratubular obstruction, vasoconstriction, inflammation, and a reduction in GFR.38

Patients with cancer should have their risk for TLS assessed before the initiation of therapy. Risk factors for TLS include those related to the tumor as well as those related to the patient (Fig. 5). There are no validated risk-scoring systems and thus clinicians should use their own judgement in classifying patients. As shown in Figure 6, those patients considered at low risk for TLS should be treated with oral hydration and avoidance of other nephrotoxic agents. For patients with higher risk, intravenous 0.9% saline or, preferably, a balanced isotonic crystalloid solution (1-2 mL/kg/hour) should be administered to maintain adequate hydration status and GFR. Hydration should be started 24 to 48 hours before therapy. Hydration will also maintain tubular flow rates that facilitate clearance and dilution of uric acid as well as the clearance of potassium and phosphate. In addition, patients at high risk for TLS should receive a xanthine oxidase inhibitor (allopurinol or febuxostat) to blunt de novo formation and increases in the concentration of uric acid by blocking the conversion of hypoxanthine and xanthine to uric acid.39

These drugs should be started 2 or 3 days before the initiation of therapy. Urinary alkalization, which increases the solubility of uric acid in the renal tubules, is not recommended because it can increase the likelihood of calcium-phosphate precipitation and symptomatic hypocalcemia.38

For patients who present for treatment with elevated uric acid levels (>8 mg/dL), treatment with recombinant urate oxidase (rasburicase) is recommended to rapidly (within 24 hours) lower uric acid levels.40 Rasburicase converts uric acid to a soluble compound (allantoin) that is readily excreted in the urine. Rasburicase does lead to the production of hydrogen peroxide in this process and thus there is a risk of methemoglobinemia and hemolytic anemia in susceptible patients (those with glucose-6-phosphate dehydrogenase deficiency).41 When patients present with established TLS, it is mandatory to monitor fluid status, electrocardiography, electrolytes, and GFR. Electrolyte disorders should be identified and corrected rapidly according to standard protocols (Fig. 6). The lowering of uric acid levels may improve GFR and ameliorate AKI, although data indicating that rasburicase promotes AKI recovery are lacking.42 For patients presenting with established AKI, especially if they are oliguric or anuric, emergent hemodialysis may be required and can correct electrolyte disorders quickly and safely. For those cases in which rasburicase is either not available or contraindicated, prophylactic hemodialysis should be considered before chemotherapy. Hemodialysis is efficient in removing uric acid; the clearance is approximately 70 to 100 mL/minute, and serum uric acid levels fall by approximately 50% with each 6-hour treatment. Continuous renal replacement may be particularly effective, avoids the risks of rebound metabolic disturbances, and should be dosed for clearances of 30 to 40 mL/kg/hour.

**Tumor Infiltration of the Kidneys**

Leukemia and lymphoma cells have a predilection for infiltrating the kidney.43 In most cases, these infiltrates are only detected on autopsy; however, in approximately 1% of cases, they may be so massive that they result in AKI.43,44 AKI in these cases likely results from compression of the surrounding renal parenchyma by tumor cells with disruption of the microvasculature and tubular structures, which impairs GFR. Patients may present with hypertension (caused by activation of the renin-angiotensin system), flank pain, and hematuria; however, more often, patients have asymptomatic AKI. Renal imaging with ultrasonography or computed tomography shows bilaterally enlarged kidney with a heterogeneous texture, representing the infiltrating cancer cells. A kidney biopsy is diagnostic and reveals tumor cell infiltration. Appropriate chemotherapy with tumor response can lead to rapid improvement in kidney function, although patients may be at high risk for TLS.

**Light-Chain Cast Nephropathy**

MM is associated with a high incidence of AKI (as high as 50%).45 The most common etiology of AKI in these patients is cast nephropathy. Other etiologies of AKI include light-chain-related proximal tubulopathy, various glomerular diseases (including light-chain deposition disease and light-chain [AL] amyloidosis), hypercalcemia, hyperuricemia, and other less common causes (Fig. 7). Cast nephropathy is caused by glomerular filtration of large amounts of free light chains (FLCs) into the renal tubules, which subsequently bind to Tamm-Horsfall protein (also known as uromodulin) to form insoluble aggregates.46 These intratubular precipitates lead to obstruction of tubular flow and local inflammation, which may be exacerbated by proximal tubular uptake of pathogenic light chains.47 Factors that promote the formation of intratubular casts include volume depletion, metabolic acidosis, loop
diuretics through the increase in tubular sodium concentration, increased urinary calcium and hypercalcemia, and radiocontrast media.\(^4^8\)

Sensitive assays for plasma FLCs as well as serum and urine protein electrophoresis and immunofixation facilitate the diagnosis of myeloma-related AKI. The normal plasma-free $\kappa$-to-$\lambda$ ratio is 0.26 to 1.65 in patients without kidney impairment and 0.37 to 3.1 in patients with severe kidney impairment.\(^4^8\) Elevated FLCs in association with an abnormal $\kappa$-to-$\lambda$ ratio typically indicate a monoclonal plasma cell proliferative process. The plasma FLC assay is more sensitive than urine protein electrophoresis for detecting FLCs.\(^4^9\) Light-chain cast nephropathy should be strongly suspected in any patient presenting with unexplained kidney impairment and an elevated FLC level $\geq 1500$ mg/L. Light-chain cast nephropathy is uncommon in patients with low (<500 mg/L) plasma FLC concentrations.\(^5^0\) It is important to note that patients with myeloma-related glomerular diseases will present with high levels of albuminuria ($>2$ g/day) indicative of the glomerular disease process, whereas patients with cast nephropathy will demonstrate high levels of urine and serum light chains and lower levels of albuminuria.\(^5^1\) Of note, 15% of patients with AKI in the setting of myeloma may have an etiology of AKI completely unrelated to myeloma, thus kidney biopsy should be performed in unclear cases.\(^5^1\)

Therapy for AKI caused by cast nephropathy focuses on a combination of aggressive intravenous hydration to enhance renal tubular flow, correction of hypercalcemia and hyperuricemia, and treatment of other precipitating or aggravating factors, and chemotherapy to rapidly lower the production of pathogenic light chains. Chemotherapeutic regimens for myeloma generally include a proteasome inhibitor, such as bortezomib (which does not require dosing adjustments for renal function).\(^5^2\) Regimens including bortezomib (usually in combination with dexamethasone and another agent, such as thalidomide or melphalan) have led to renal response rates as high as 72% and dialysis discontinuation in 57% of patients.\(^5^2\) Other effective agents include thalidomide, lenalidomide, pomalidomide, and carfilzomib.\(^5^3\) It has been demonstrated that a clinically significant reduction in FLCs within 3 weeks is associated with a greater likelihood of partial or full renal recovery.\(^5^4\) HSCT is a viable option for patients with AKI, even those on dialysis. Although the likelihood of a hematologic response is good in these patients, renal recovery is unlikely.\(^5^5\)

As discussed above, the recognition that a rapid reduction in plasma FLC levels is associated with an improved prognosis has driven studies investigating whether extracorporeal (through high-flux hemodialysis or therapeutic plasmapheresis) removal of plasma FLCs leads to improved outcomes.
A great deal of controversy remains surrounding the benefit of removing light chains with these modalities. High-cutoff hemodialysis uses prolonged dialysis sessions (6–8 hours) with a hemofilter that has a large pore size, which allows for the effective clearance of plasma FLCs. Early, nonrandomized clinical studies showed both a significant reduction in plasma FLC levels and improved kidney function. More recently, 2 randomized clinical trials have used high-cutoff hemodialysis in the context of bortezomib-based chemotherapy to assess the effect on clinical outcomes. The Multiple Myeloma and Renal Failure Due to Myeloma Cast Nephropathy (MYRE) trial randomized 98 patients with biopsy-proven cast nephropathy requiring dialysis to either intensive high-flux hemodialysis or high-cutoff hemodialysis (consisting of 5-hour sessions). All patients received bortezomib-based chemotherapy. There was no significant difference in the primary endpoint of dialysis independence at 3 months between the control and high-cutoff hemodialysis groups (33% vs 43%, respectively; \( P = .42 \)), although the median reduction rate of FLCs after the first dialysis session was significantly higher in the high-cutoff hemodialysis group (68%) compared with the control group (31%; \( P = .001 \)). Of note, in a secondary analysis, more patients in the high-cutoff hemodialysis group were dialysis-free at 6 months (56.5% \( [n = 26] \) vs 35.4% \( [n = 17] \); \( P = .04 \)) and at 12 months (60.9% vs 37.5%; \( P = .02 \)). Dialysis independence at 12 months was associated with a decrease in serum FLC concentration to <500 mg/L with the first round of chemotherapy (\( P = .01 \)) and randomization to high-cutoff hemodialysis (\( P = .02 \)). The European Trial of Free Light Chain Removal by Extended Hemodialysis in Cast Nephropathy (EuLITE) randomized 90 patients with cast nephropathy and dialysis-requiring AKI to either high-flux hemodialysis or extended high-cutoff hemodialysis. Similar to the MYRE trial, all patients...
received bortezomib-based therapy. The primary outcome was independence from dialysis at 90 days. After 90 days, 24 (56%) patients in the high-cutoff hemodialysis group and 24 (51%) patients in the high-flux hemodialysis group were independent from dialysis (relative risk, 1.09; 95% CI, 0.74-1.61; \( P = .81 \)). Thus high-cutoff hemodialysis did not improve clinical outcomes and increased complications in this patient group. Given the findings of these 2 trials, the use of high-cutoff hemodialysis for rapid removal of plasma FLCs cannot be routinely recommended. Similarly, the removal of FLCs with plasmapheresis in improving renal prognosis and patient survival remains to be determined but is not routinely recommended.69

Urinary Tract Obstruction
Obstruction of the urinary tract is a common etiology of AKI in the patient with cancer. Obstruction can be intraluminal because of precipitation of uric acid (as in TLS) or from medications such as high-dose methotrexate or high-dose intravenous acyclovir. More commonly, urinary tract obstruction is extraluminal and is caused by compression of the ureters by tumor mass (such as with cervical carcinoma) or by prostatic disease compressing the urethra. The clinical spectrum of patients presenting with malignant ureteral obstruction was illustrated by a case series of 102 patients.60 Obstruction was bilateral in 68% of patients, and initial management with a percutaneous nephrostomy or ureteral stent was successful in 95%. Despite successful decompression, 53% of patients developed complications, mostly urinary tract infection and obstruction of nephrostomy tubes or stents, and overall survival was poor (median survival, 7 months), reflecting the advanced stage of malignancy in such patients. Renal ultrasonography will usually demonstrate hydronephrosis in patients with obstruction. However, for unclear reasons, in patients who have retroperitoneal fibrosis or retroperitoneal lymph node infiltration by cancer (eg, lymphomas and leukemias) or cancers that are more commonly associated with retroperitoneal spread (prostate, colon, bladder, cervical, and ovarian), hydronephrosis may be lacking; and, if clinical suspicion is high for this condition, other imaging techniques such as nuclear medicine scans should be pursued.61 On several occasions, if the suspicion is high despite normal imagining for hydronephrosis, decompression procedures might be required for diagnostic and therapeutic purposes in such cases.

Thrombotic Microangiopathy
Thrombotic microangiopathy (TMA) is characterized by microangiopathic hemolytic anemia from red blood cell fragmentation (schistocytes, increased lactate dehydrogenase, depressed haptoglobin), thrombocytopenia (platelet count <150,000 mm\(^3\) or >30% reduction) and end-organ damage, including AKI.62 Malignancies and their therapies constitute important secondary causes of TMA.62 HSCT is also associated with TMA.62,63

TMA can present with AKI, new or acute worsening of hypertension, proteinuria, and active urinary sediment. AKI is often severe and may ultimately require dialysis.62,63 Kidney histology reveals endothelial cell swelling, fibrin thrombi within capillary loops and arterioles, fragmented red blood cells, mesangiosis, and thickened arterioles and glomerular capillaries.62,63

Certain cancers, especially when metastatic, more frequently cause TMA compared with others—these include mucinous gastric cancers, ovarian cancers, lymphomas, and acute myeloid leukemias.64 More recently, cancers associated with a monoclonal gammapathy, including plasma cell dyscrasias and B-cell lymphoproliferative disorders, were recognized as being associated with TMA.65 There are several possible mechanisms for TMA. Mucin-producing adenocarcinomas may directly injure vascular endothelium, impairing production and release of von Willebrand factor.66 Disseminated cancers with microvascular embolic tumor cells can injure red blood cells, inducing inflammation and activating platelets, thereby promoting microthrombosis and/or TMA.67 Complement activation can also play a role in the development of cancer-related TMA. Upregulation of complement genes has been described in endometrial tissue from patients with ovarian cancer and lung tissue from patients with lung cancer who developed thrombosis.68 Direct complement activation via the lectin pathway was described in adult T-cell lymphoma through the activation of galactomannan on tumor cell membranes.69 Furthermore, thrombin generation by certain cancers may perpetuate thrombosis and potentially provoke TMA by cleaving C5 and activating the complement system.70 Eradication of the cancer is often associated with TMA resolution; however, TMA may redevelop upon recurrence of some cancers.64

Cancer therapies are a relatively common cause of TMA.71 Clinical clues that suggest drug-induced TMA include a temporal association between drug initiation and development of the clinical syndrome and partial/complete recovery of the microangiopathic process after drug withdrawal.71 Cancer drug-induced TMA more closely resembles hemolytic uremic syndrome, and a renal-limited form of TMA is not unusual with certain drugs. Direct vascular endothelial injury, increased platelet activation/aggregation, and alternative complement pathway disorders may play a role in drug-induced TMA. Cancer drugs may initiate TMA as a second hit in patients with underlying genetic defects in the alternative complement cascade, such as factor H, factor I, factor B, membrane cofactor protein, thrombomodulin, and C3 complement.72
| MEDICATION                                | CLINICAL RENAL SYNDROME                                                                 | RENAL HISTOPATHOLOGY                                      |
|------------------------------------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------|
| Conventional chemotherapy                |                                                                                         |                                                          |
| Platinum compounds (cisplatin, carboplatin, oxaliplatin) | • Acute kidney injury  
• Hypomagnesemia  
• Nephrogenic diabetes insipidus  
• Proximal tubulopathy  
• Salt wasting | • Acute tubular injury  
• Thrombotic microangiopathy | |
| Ifosfamide                                | • Acute kidney injury  
• Nephrogenic diabetes insipidus  
• Proximal tubulopathy | • Acute tubular injury | |
| Methotrexate                              | • Acute kidney injury  
• Hematuria/proteinuria  
• Hypertension | Crystalline nephropathy  
• Acute tubular injury | |
| Gemcitabine                               | • Acute kidney injury  
• Hematuria/proteinuria  
• Hypertension | Thrombotic microangiopathy | |
| Nitrosoareas                              | • Chronic kidney disease                                                                | Chronic tubulointerstitial nephritis | |
| Targeted cancer agents                    |                                                                                         |                                                          |
| Anti-VEGF agents (aflibercept, bevacizumab) | • Acute kidney injury  
• Hypertension  
• Proteinuria | Thrombotic microangiopathy  
• Acute tubular injury | |
| Tyrosine kinase inhibitors (axitinib, pazopanib, sorafenib, regorafenib, sunitinib) | • Acute kidney injury  
• Hypertension  
• Proteinuria | Focal segmental glomerulosclerosis  
• Thrombotic microangiopathy  
• Acute tubulointerstitial nephritis  
• Acute tubular injury | |
| BRAF inhibitors (dabrafenib, vemurafenib) | • Acute kidney injury  
• Electrolyte disorders | Acute tubulointerstitial nephritis  
• Acute tubular injury | |
| ALK inhibitors (crizotinib)               | • Acute kidney injury  
• Electrolyte disorders  
• Acquired kidney microcysts | Acute tubulointerstitial nephritis  
• Acute tubular injury | |
| EGFR inhibitors (cetuximab, erlotinib, gefitinib, panitumumab) | • Hypomagnesemia  
• Hypokalemia and hypocalcemia due to hypomagnesemia | None | |
| Bcr-abl tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib) | • Acute kidney injury  
• Chronic kidney disease | Acute tubulointerstitial nephritis  
• Acute tubular injury | |
| Rituximab                                 | • Acute kidney injury  
• Tumor lysis syndrome | Acute tubular injury  
• Uric acid nephropathy | |
| Cancer immunotherapies                    |                                                                                         |                                                          |
| Interferons (α, β, γ)                     | • Acute kidney injury  
• Nephrotic-range proteinuria | Focal segmental glomerulosclerosis  
• Thrombotic microangiopathy | |
| Interleukin-2                             | • Acute kidney injury  
• Capillary leak syndrome | Hemodynamic  
• Acute tubular injury | |
| Chimeric antigen receptor T-cells (CAR-T)  | • Capillary leak syndrome  
• Acute kidney injury  
• Tumor lysis syndrome  
• Electrolyte disorders | Hemodynamic  
• Acute tubular injury  
• Uric acid nephropathy (?) | |
| CTLA-4 inhibitors (ipilimumab, tremelimumab) | • Acute kidney injury  
• Proteinuria | Acute tubulointerstitial nephritis  
• Acute tubular injury  
• Lupus-like glomerulonephritis  
• Minimal change disease  
• Necrotizing glomerulonephritis and vasculitis  
• Thrombotic microangiopathy | |
Loss or inhibition of vascular endothelial growth factor (VEGF) induces renal-limited TMA, suggesting a protective role for VEGF against glomerular endothelial injury. Loss of VEGF promotes endothelial dysfunction and injury, leading to TMA. A recent study suggested that a reduction in podocyte-synthesized VEGF by pharmacological VEGF inhibition or genetic ablation decreases local inhibitory complement factor H and other complement regulators in the renal glomerulus, increasing vulnerability to complement activation and development of TMA.

Cancer drugs that cause TMA include conventional chemotherapeutics (gemcitabine, mitomycin, cisplatin) and targeted agents (anti-VEGF drugs, proteasome inhibitors). Conventional agents cause more severe, dose-dependent TMA, which is associated with increased morbidity and mortality. For example, gemcitabine-induced TMA is a rare complication (incidence, 0.015%-0.31%) but maintains a high mortality rate (range, 40%-90%). Traditional therapies such as plasma exchange have not been successful in treating gemcitabine-induced TMA. Case reports and series suggest that complement inhibition may be a reasonable therapy for gemcitabine-associated TMA.

Targeted drug-related TMA is generally less severe and is associated with better kidney function recovery after drug discontinuation. For example, VEGF pathway inhibitors are another cause of drug-induced TMA. Monoclonal antibodies targeting the VEGF pathways and tyrosine kinase inhibitors have been linked to hypertension, proteinuria, AKI, and TMA. Anti–VEGF-ligand exposure was associated with biopsy-proven TMA in >100 patients from a single-center case series. Approximately 50% of TMA cases from >100 that were biopsied for kidney disease (proteinuria and/or abnormal kidney function) were renal-limited, which is greater than other drug-induced causes of TMA. Anti-VEGF drug withdrawal and blood pressure control (with a renin-angiotensin-aldosterone system blocker) are often associated with significant kidney function improvement. Proteasome inhibitors are less commonly associated with TMA. TMA associated with HSCT is discussed below.

Drug-Associated Nephrotoxicity
Anticancer drugs are an important cause of AKI and other adverse kidney events (Table 1). AKI associated with conventional chemotherapeutic agents is caused primarily by acute tubular toxicity, acute tubulointerstitial nephritis (ATIN), and various glomerular injuries. In addition to conventional agents, the emergence of cancer immunotherapies and targeted cancer therapies has increased the occurrence of drug-induced AKI in patients with cancer.

### Table 1. (Continued)

| MEDICATION | CLINICAL RENAL SYNDROME | RENAL HISTOPATHOLOGY |
|------------|------------------------|----------------------|
| PD-1 inhibitors (nivolumab, pembrolizumab, cemiplimab) | • Acute kidney injury • Proteinuria | • Acute tubulointerstitial nephritis • Acute tubular injury • Minimal change disease • IgA nephropathy • Focal segmental glomerulosclerosis • Necrotizing glomerulonephritis and vasculitis • AA amyloidosis • Electrolyte abnormalities |
| PD-L1 inhibitors (atezolizumab, avelumab, durvalumab) | • Acute kidney injury | • Acute tubulointerstitial nephritis |
| Other drugs | | |
| Bisphosphonates (pamidronate, zoledronate) | • Acute kidney injury • Nephrotic syndrome | • Acute tubular injury • Focal segmental glomerulosclerosis • Minimal change disease |
| Sirolimus | • Acute kidney injury • Proteinuria | • Focal segmental glomerulosclerosis |

Abbreviations: AA, secondary amyloidosis CTLA-4, cytotoxic T-lymphocyte-associated protein-4; EGFR, epidermal growth factor receptor; PD-1, programmed death-1; PD-L1, programmed death ligand-1; VEGF, vascular endothelial growth factor.
agent that is complicated by dose-limiting nephrotoxicity.\textsuperscript{86,87} After drug entry into proximal tubular cells through the organic cation transporter, direct tubular toxicity occurs because of several intracellular injury pathways. In the intracellular compartment, chloride ions are replaced with water molecules in the cis-position of cisplatin, forming hydroxyl radicals that injure neutrophilic binding sites on DNA.\textsuperscript{86,87} AKI then results from renal tubular apoptosis and necrosis, which typically develop approximately 3 to 5 days after drug exposure. Although AKI is generally reversible, repeated cisplatin doses (>100 mg/m\textsuperscript{2}) may cause permanent kidney injury. Isotonic or hypertonic saline administration and avoidance of other nephrotoxins most effectively prevent cisplatin-induced nephrotoxicity. Amifostine, by improving DNA repair and elimination of free radicals, may reduce cisplatin injury; however, its use has been limited by adverse side effects such as hypotension and nausea/vomiting.\textsuperscript{86,87} Carboplatin and oxaliplatin are less nephrotoxic than cisplatin but can still cause AKI in at-risk patients.\textsuperscript{90}

The alkylating agent ifosfamide is also associated with renal tubular injury, especially when combined with platinum drugs. Like cisplatin, this drug enters proximal tubular cells via the organic cation transporter.\textsuperscript{86,87} Ifosfamide and its metabolite chloracetaldehyde cause direct tubular epithelial cell damage by multiple mechanisms, including DNA injury, reactive oxygen species generation, ATP depletion, and increased intracellular calcium.\textsuperscript{86,87} Ifosfamide-induced tubular injury is associated with AKI and proximal tubule dysfunction, including Fanconi syndrome.\textsuperscript{91} Risk factors for ifosfamide-related AKI include previous cisplatin exposure, underlying CKD, and high cumulative doses (>84 g/m\textsuperscript{2}).\textsuperscript{92} Most patients recover from ifosfamide-induced tubular injury; however, CKD and permanent tubular dysfunction may develop.\textsuperscript{86,87}

Methotrexate is often administered in high doses (>1 g/m\textsuperscript{2}).\textsuperscript{86,87,91,92} Precipitation of insoluble parent drug and metabolites (7-OH methotrexate) within tubular lumens leads to AKI from crystalline nephropathy.\textsuperscript{86,87,93,94} True or effective volume depletion and acidic urine are major risk factors for crystalline-associated AKI. Direct tubular toxicity from methotrexate-induced decreases in adenosine deaminase activity promotes oxygen free-radical formation, resulting in cellular injury, and may contribute to the development of AKI. The overall cumulative incidence rate of AKI is approximately 1.8% (range, 0%-12%) but is as high as 50% in at-risk patients.\textsuperscript{93,94} In general, kidney injury is reversible. Preventive measures include volume repletion to achieve high urine flow rates as well as urine alkalinization (pH >7.5). Once AKI develops, methotrexate excretion is reduced, and systemic toxicity may occur. Supportive care along with high-dose leucovorin therapy can reduce the systemic toxicity. Prolonged hemodialysis (6 hours) can reduce plasma methotrexate levels by approximately 70% but, because of rebound, must be performed daily for several days.\textsuperscript{95} Despite dialysis, levels may still remain in the toxic range. Glucarpidase, an enzyme that inactivates methotrexate, is an option when AKI and severe systemic toxicity occur.\textsuperscript{96}

**Cancer immunotherapies**

Drugs that modulate the immune system have been used in cancer therapy for several decades. These include interferon and interleukin-2 (IL-2) and, more recently, immune-checkpoint inhibitors (ICPIs) and chimeric antigen receptor T-cells (CAR-Ts) (Table 1).

Interferon therapy is used for some cancers but may be complicated by AKI and high-grade proteinuria from focal segmental glomerulosclerosis (FSGS) or minimal change disease (MCD), which develop after many weeks to months of drug exposure.\textsuperscript{97,98} Drug discontinuation and possible use of corticosteroids are fairly effective for recovery of kidney function with MCD, but not with FSGS.\textsuperscript{97,98}

High-dose IL-2 has been used to treat renal cell carcinoma (RCC), malignant melanoma, and other cancers. It is associated with a cytokine release syndrome (CRS) and capillary leak, causing a prerenal form of AKI that develops within 24 to 48 hours.\textsuperscript{99} AKI generally reverses with drug discontinuation, although ischemic/nephrotic acute tubular injury can be associated with a more prolonged course of AKI.\textsuperscript{99}

ICPIs leverage the immune system against cancer.\textsuperscript{89} To maintain immune homeostasis, host T cells express receptors such as cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) and programmed death-1 protein (PD-1), whereas host tissues express programmed death ligand-1/programmed death ligand-2 (PD-L1/PD-L2), which ultimately downregulate T-cell function.\textsuperscript{89,100} These immune checkpoints act to balance appropriate immune activation against the development of potentially harmful autoimmunity. Tumors capitalize on these immune checkpoints by overexpressing ligands that bind inhibitory CTLA-4 and PD-1 receptors—an effect that decreases T-cell infiltration into the tumor microenvironment and inhibits antitumor T-cell responses.\textsuperscript{101} To combat this, monoclonal antibody drugs that block ligand binding to PD-1 and CTLA-4 receptors were designed to facilitate T-cell rescue and restore antitumor immunity. Ipilimumab and tremelimumab are humanized monoclonal antibodies against CTLA-4, whereas nivolumab, pembrolizumab, and cemiplimab are humanized monoclonal antibodies against PD-1 receptors.\textsuperscript{101} In addition, humanized monoclonal antibodies (atezolizumab, avelumab, durvalumab) target PD-L1.\textsuperscript{101}

The success of ICPI therapy is fraught with the development of autoimmunity and end-organ injury such as AKI.\textsuperscript{101-103} The reported incidence of overall AKI ranges
between 2% and 17% but is closer to 2% or 3% when biopsy-proven or clinically adjudicated. Development of AKI after ICPI exposure occurs from several weeks to many months after drug initiation. Although various kidney lesions have been described, over 100 cases of biopsy-proven ATIN have been observed with ICPIs. Clinical and laboratory manifestations are neither sensitive nor specific to diagnose ATIN as the cause of AKI. Less than one-half of patients have extrarenal immune-related adverse effects in the setting of ATIN. We recommend kidney biopsy for stage 2 and 3 AKI; however, a trial of corticosteroids may be considered without biopsy in some patients. Even in the absence of ATIN on biopsy, drug withdrawal (>90%) and corticosteroids (>80%) are commonly used to treat AKI. Approximately one-third of patients completely recover kidney function, while slightly less than one-half have partial kidney function recovery. A few patients have required dialysis, which can be permanent. ICPI re-challenge after AKI is associated with AKI relapse in approximately one-quarter of patients.

CAR-Ts are host cells that are harvested and engineered to express receptors that recognize and bind tumor antigens (such as CD19, CD20, or CD30) without requiring traditional antigen presentation to the T-cell receptor. They are currently approved to treat refractory lymphomas and leukemias. These T cells directly target and efficiently destroy cancer cells. As seen in CAR-T trials, CRS is a common complication, although other toxicities can occur. AKI was noted in 17% to 24% of patients. CRS and macrophage activation can result in severe capillary leak and AKI because of hemodynamic effects or acute tubular injury. A recent study in 78 patients treated with CAR-Ts for lymphoma noted CRS in 85% of patients and AKI in 19%. AKI was due primarily to hemodynamic effects and ATIN. AKI may also occur because of TLS. Prevention and treatment of AKI include chemotherapy and corticosteroids before CAR-T exposure to reduce the tumor burden as well as standard supportive care in critical care units. With severe CRS, an IL-6 receptor blocker may reduce adverse systemic effects.

**Targeted cancer therapies**

Drugs that target mutated or overexpressed oncoproteins in cancers are also complicated by adverse renal effects (Table 1). Antiangiogenesis drugs effectively treat several cancers through inhibition of the VEGF pathway. By disrupting the VEGF pathway, these drugs lead to glomerular and peritubular capillary endothelial cell dysfunction, resulting in TMA and AKI. The reader is referred to the section above for a discussion of the anti-VEGF drugs as a cause of TMA. These drugs can also cause AKI from acute tubular injury as well as ATIN (rare cases). As described in a meta-analysis of 7 trials, these drugs increase the occurrence of hypertension with a relative risk of 3-fold to 7-fold and a cumulative incidence between 17% and 80%. Adverse kidney effects such as AKI developing with these drugs may require dose reduction or drug discontinuation.

Selective B-RAF inhibition by vemurafenib and dabrafenib is effective against malignant melanoma, which frequently has a B-RAF V600 mutation. These drugs have also been observed to cause nephrotoxicity. A reduction in eGFR developed at 1 and 3 months of therapy in 15 of 16 patients treated with these drugs. Eight patients also developed AKI (acute tubular injury on biopsy in one patient) after vemurafenib therapy. Four of the patients with AKI who were treated with vemurafenib were thought to have ATIN (no biopsy data), with 3 of 4 patients recovering kidney function after drug discontinuation. Of 74 patients who were treated with vemurafenib, approximately 60% developed AKI, primarily KDIGO stage 1, within 3 months of drug exposure. Biopsy in 2 patients revealed tubulointerstitial injury; kidney function recovered within 3 months of B-RAF discontinuation. Although the mechanism of kidney injury is unknown, these drugs may increase susceptibility to ischemic tubular injury by interfering with the downstream mitogen-activated protein kinase (MAPK) pathway.

Small-molecule inhibitors of anaplastic lymphoma kinase-1 (ALK-1) include crizotinib and ceritinib. Crizotinib is an effective agent for advanced ALK-positive nonsmall cell lung cancer; however, it is complicated by AKI as well as renal cyst development and progression. Crizotinib is associated with both true AKI from tubulointerstitial injury and pseudo-AKI from drug-induced reduction in proximal tubular creatinine secretion.

**AKI After Nephrectomy for RCC**

Many RCCs are found incidentally with abdominal imaging. The percentage of kidney cancers <7 cm in size and confined to the kidney has increased from 43% to >60%. At the same time, 5-year survival has improved to >90% for patients who have T1 tumors and is nearly 100% for those who have tumors <4 cm after surgical resection. However, surgical resection is associated with a risk of AKI, with a reported rate up to nearly 60%, depending on underlying risk factors. Thus, given the high RCC cure rate and the underlying risk for AKI (and CKD), current management focuses on preoperative risk assessment and nephron-preserving surgery.

Numerous studies clearly demonstrate that AKI develops after either radical nephrectomy (RN) or partial nephrectomy (PN), including robotic surgery. Although postprocedure AKI occurs more commonly when CKD and other
comorbidities such as older age, hypertension, diabetes, and solitary kidneys are present before surgery, patients with normal kidney function can also develop AKI. As such, preoperative screening using KDIGO CKD criteria (eGFR and albuminuria) is recommended for patients at risk for AKI. Measures such as stopping/avoiding potential nephrotoxic medications as well as ensuring adequate intraoperative kidney perfusion reduce the risk for postnephrectomy AKI.

Although PN achieves comparable oncologic and overall survival compared with RN, the AKI rate is higher with RN. As such, PN is recommended whenever technically feasible to preserve nephron mass and is the preferred surgical option for T1 RCCs. Ablative techniques may decrease the incidence of AKI further, but more data are required to assess long-term oncologic outcomes, so careful patient selection is essential.

Kidney Disease Associated With HSCT
AKI remains common in the setting of HSCT and increases the risk of in-hospital morbidity and mortality. In addition, TMA is a common finding in patients who develop CKD in this population. Figure 8 summarizes the various forms of kidney diseases seen with HSCT.

Acute Kidney Injury with HSCT
HSCT requires induction chemotherapy with or without total body irradiation, followed by bone marrow rescue by engraftment of stem or progenitor cells, which are harvested from bone marrow, peripheral blood, or umbilical cord blood. Stem or progenitor cells may come from the affected patient (autologous) or from a sibling or unrelated donor (allogeneic; both myeloablative and nonmyeloablative). AKI has been described with different frequencies in both autologous and allogeneic HSCT. The incidence, as noted in Table 2, is much lower in autologous HSCT. The wide variation noted in AKI incidence is likely because of the retrospective nature of most studies and the different criteria used for defining AKI. The incidence of AKI varies from 12% to 50% in autologous HSCT to 19% to 66% in allogeneic HSCT. The median time to onset of AKI is 10 to 40 days after transplantation. Morbidity and mortality associated with AKI in HSCT are high. HSCT recipients who develop AKI have an increased risk of death within the first 6 months post-HSCT. The 5-year survival rate for HSCT recipients who develop AKI is 20% lower than the rate for those without AKI. Patients with AKI who require dialysis also have worse outcomes, with mortality approaching >80% (Table 2).

Table 3 summarizes the various risk factors described in the literature for AKI after HSCT. The various etiologies of AKI are shown in Figure 8. Both sepsis and antimicrobial agents may increase the risk of AKI. Amphotericin, intravenous acyclovir, and vancomycin with piperacillin/tazobactam (combination) are associated with AKI. Calcineurin inhibitors (CNIs) play a major role as contributors to AKI after HSCT. Calcineurin inhibitors (CNIs) play a major role as contributors to AKI after HSCT.

FIGURE 8. Etiologies of Acute Kidney Injury and Chronic Kidney Disease With Hematopoietic Stem Cell Transplantation. BK indicates BK polyomavirus.
be triggered by factors such as hypotension, sepsis, or exposure to nephrotoxic agents. Evidence of intrinsic kidney injury has not been seen on kidney biopsies or autopsies from patients with VOD, consistent with the understanding that VOD-associated AKI is most likely hemodynamic, similar to hepatorenal syndrome. Mortality rates with severe AKI are high, approaching 40% and 85% in patients with a doubling of serum creatinine and those requiring dialysis, respectively.139 Although mortality is high in patients with VOD and moderate-to-severe AKI, the majority of the patients with VOD recover with supportive therapy, which includes attention to fluid balance (edema and ascites management), monitoring daily fluid intake/output and weights is important for preventing and mitigating fluid overload. In those patients who may need dialysis, the timing of initiation of this therapy remains controversial.

### Chronic Kidney Disease With HSCT

The incidence of CKD after HSCT has been reported to vary between 10% and 66%.146 This wide variation is likely caused in part by the use of different definitions of kidney dysfunction, duration of follow-up, and type of transplantation. Importantly, stem cell transplantation recipients develop ESKD at a rate far higher than that seen in the general population, and the incidence of CKD after transplantation is anticipated to rise as the age of patients receiving stem cell transplantation continues to increase.147,148 A retrospective study of 158 patients who survived ≥3 years after myeloablative transplantation showed that 17% developed CKD stage ≥3.149 Another retrospective study over ≥10 years in 77 patients who underwent myeloablative allogeneic transplantation found that the cumulative incidence of CKD (defined as a persistent decrease in eGFR <60 mL/minute/1.73 m²) increased over time, reaching 34% at 10 years.150 Table 3 lists the risk factors for CKD associated with HSCT.

### Thrombotic Microangiopathy After HSCT

TMA often presents as AKI but is also a cause of CKD (anywhere from 2.3% to 30%) in patients who undergo HSCT.151,152 Emerging data reveal that transplantation-associated TMA might be a complication of graft-versus-host disease (GVHD) and its therapy.153 For patients with post-HSCT.142-144 Both of these viruses cause hemorrhagic cystitis and interstitial nephritis. Management usually is supportive, but there have been some successful cases of intra-vesical cidofovir therapy for adenovirus-related illnesses. The standard treatment for BK nephropathy is to reduce immunosuppression. Cidofovir, brincidofovir, and leflunomide have also been used as possible antiviral therapies with modest success, but they are associated with significant toxicities.145

Treatment of AKI in HSCT is frequently supportive. Holding nephrotoxic medications, using viral surveillance, and treating infections with early recognition of sepsis in the immunocompromised host may lead to improvement in kidney function. Meticulous attention to fluid management by monitoring daily fluid intake/output and weights is important for preventing and mitigating fluid overload. In those patients who may need dialysis, the timing of initiation of this therapy remains controversial.

### TABLE 2. Types of Hematopoietic Stem Cell Transplantations and Kidney Complications

| CONDITIONING REGIMEN | DONOR RELATIONSHIP | CALCINEURIN EXPOSURE | RISK OF GVHD | RISK OF ACUTE KIDNEY INJURY, % | RISK OF ACUTE KIDNEY INJURY REQUIRING DIALYSIS, % | RISK OF MORTALITY IF NEEDED DIALYSIS, % |
|----------------------|--------------------|----------------------|-------------|-------------------------------|---------------------------------------------|----------------------------------------|
| Myeloablative        | Allogeneic         | High                 | Very high   | 19-66                         | 17                                          | >80                                    |
| Nonmyeloablative     | Allogeneic         | High                 | High        | 29-54                         | 4                                           | >80                                    |
| Nonmyeloablative     | Autologous         | None                 | None        | 12-50                         | 4                                           | 70                                     |

### TABLE 3. Risk Factors for Acute Kidney Injury and Chronic Kidney Disease Associated With Hematopoietic Stem Cell Transplantation

| Risk factors for acute kidney injury: |
|--------------------------------------|
| Female sex, diabetes mellitus, pretransplantation serum creatinine >0.7 mg/dL |
| Hypertension, early weight gain >2 kg, veno-occlusive disease |
| GVHD grade 3-4, sepsis, jaundice, lung toxicity |
| Etoposide-based induction, admission to intensive care unit |
| Amphotericin B use, aminoglycosides (eg, gentamicin), calcineurin inhibitors (cyclosporine, tacrolimus), intravenous immunoglobulins |
| Risk factors for chronic kidney disease: |
| Previous AKI, older age, lower pretreatment GFR, female sex, fludarabine conditioning |
| GVHD, calcineurin inhibitor exposure |
| TMA, glomerular diseases |
| Total body radiation, hypertension, albuminuria |

Abbreviations: AKI, acute kidney injury; GFR, glomerular filtration rate; GVHD, graft-versus-host disease; TMA, thrombotic microangiopathy.
significant transplantation-associated TMA who are on CNIs or mTOR inhibitors as part of their GVHD prophylaxis, replacing them with alternative GVHD prophylactic agents, such as steroids, mycophenolate mofetil, IL–2 inhibitors, or anti-CD20 agents, might be helpful in some cases. There are emerging data on the use of rituximab and eculizumab in the treatment of transplantation-associated TMA.154

Glomerular Diseases Associated With HSCT

Nephrotic syndrome after HSCT is a rare occurrence. Typically, this syndrome develops more than 6 months after transplantation and is related to tapering of immunosuppressive agents. The most common glomerular pathologies encountered are membranous nephropathy (MN) and MCD.155

Huang et al published the clinical course of 5 patients who had proteinuria after undergoing HSCT. All 5 had MN and evidence of chronic GVHD in remission.156 Circulating autoantibodies to podocyte transmembrane glycoprotein M-type phospholipase A2 receptor (PLA2R) are seen in a majority of cases of adult primary MN.157 In the series by Huang and colleagues, 4 patients tested negative for anti-PLA2R antibodies, suggesting that the pathogenesis of HSCT-related MN may be unique.156 In the largest retrospective series of HSCT-associated nephrotic syndrome (95 patients), chronic GVHD was common among HSCT recipients who had glomerular disease.158 A substantial proportion of patients (40%) in that series developed glomerular disease while on immunosuppressive medication, and nearly one-third of the patients were diagnosed with glomerular disease in the absence of concomitant GVHD. Similarly, another study reported a high incidence of nephrotic syndrome in a cohort of 163 patients undergoing nonmyeloablative HSCT from related HLA-compatible donors. Seven of the 163 patients in that study developed nephrotic syndrome (4 with MN).159,160

MCD is the second most common pathologic diagnosis seen in HSCT recipients with nephrotic syndrome. Although the data are limited, most cases of nephrotic syndrome respond to increasing immunosuppression according to standard guidelines used to treat these diseases.

End-Stage Kidney Disease After HSCT

Patients who progress to ESKD and require dialysis after HSCT generally do poorly compared with those who develop ESKD from other causes. In a single-center, retrospective study of 1341 patients who underwent HSCT between 1985 and 2007, 19 patients (1.4%) developed ESKD at a median of 7 years, which was 16 times higher than the expected age-adjusted rate.160 Patients who developed ESKD post–HSCT had significantly decreased survival compared with non–HSCT diabetic patients with ESKD who were matched for age and start date of dialysis.161 However, a recent study showed that patients with myeloma who were receiving dialysis and underwent an autologous HSCT did fairly well.162 Kidney transplantation remains a good option for patients with ESKD who are in prolonged cancer remission. If a patient is to receive a kidney allograft from the same donor as the original HSCT, they will likely need minimal to no immunosuppression.163 Studies have shown that these patients have a good short-term survival.

Paraneoplastic Diseases of the Glomerulus

Glomerular diseases are associated with many solid and hematologic malignancies. These glomerular lesions are thought to be paraneoplastic; however, in most cases, the exact pathogenesis is unclear.164 The treatment of these cancer-associated glomerular diseases is primarily directed at the underlying malignancy. In addition, increased cancer incidence rates are seen among patients with many different types of glomerular diseases. This increased incidence was mainly limited to a year after the diagnostic kidney biopsy, but skin cancer showed an increased risk over time that may be related to the use of immunosuppressant drugs. The risk of developing cancer 0 to 3 years after kidney biopsy for patients aged 45 to 64 years varied from 7.3% to 15.8% and, for those aged >64 years, it varied from 11.8% to 20.3%.165 Figure 9 summarizes the various glomerular diseases and respective cancers associated with them.166

Solid Tumor-Associated Glomerular Diseases

Membranous nephropathy

MN is the most common glomerular pathology described in patients with solid tumors. In the largest systematic review of 240 patients with biopsy-proven MN, Lefaucheur et al reported a prevalence of malignancy of 10%.167 Only approximately one-half of these patients had symptoms related to cancer at the time of kidney biopsy. Also, most of these patients were diagnosed with malignancy within a year of MN diagnoses. The solid tumors most commonly associated with MN are lung and gastric cancers, followed by RCC, prostate cancer, and thymoma. Other cancers reported with MN are colorectal, pancreatic, esophageal, and hepatic carcinomas.168

Circulating autoantibodies to podocyte transmembrane glycoprotein M-type phospholipase A2 receptor (a marker for primary MN in up to 80% or more of cases) were not found in patients with cancer who had secondary MN. More recent studies have shown that antibodies against thrombospondin type 1 domain-containing 7A (THSD7A) may be associated with cancer-related membranous glomerulonephritis.169 In patients with MN, it is reasonable to perform routine age-appropriate and sex-appropriate screening for malignancy. The risk of cancer persists for >5 years from the time of kidney biopsy.
Other glomerular diseases in solid tumors
MCD has been reported in association with solid tumors like lung cancer, colorectal cancer, RCC, and thymoma and rarely in pancreatic, bladder, breast, and ovarian cancers. Immunoglobulin A nephropathy can also be associated with cancers such as RCC and solid tumors of the respiratory tract, buccal mucosa, and nasopharynx. Crescentic or rapidly progressive glomerulonephritis has been associated with RCC, gastric cancer, and lung cancer. Table 4 list features of glomerular diseases consistent with a paraneoplastic process.

Hematologic Cancer-Associated Glomerular Diseases
Minimal change disease and FSGS
MCD is associated with classic Hodgkin lymphoma, and it can present around the time of diagnosis of lymphoma or preceding it by several months. A poor response to treatment of MCD with steroids, CNIs, and rituximab should raise suspicion of such a secondary cause of MCD. The pathogenesis of MCD is thought to be associated with Th2-related cytokines such as IL-13 that are overexpressed in lymphoma. FSGS has also been reported with classic Hodgkin lymphoma, usually with good a response of both to chemotherapy.

Glomerular Diseases Associated With Myeloproliferative Disorders
Glomerular disorders associated with myeloproliferative disorders are usually late complications and tend to have a poor renal prognosis, with progressive kidney injury occurring in most patients. Essential thrombocythemia and polycythemia vera have been associated with FSGS and mesangial proliferative glomerular disease. The prevalence of glomerular disease in polycythemia vera and essential thrombocytopenia is approximately 3% to 4%.

Glomerular Diseases With Special Hematologic Malignancies
Various glomerular diseases have been associated with chronic lymphocytic leukemia, with the most frequently reported findings of membranoproliferative glomerulonephritis (36%) and MN (19%). Although specific percentages are not available, large numbers of patients also have chronic lymphocytic leukemia with amyloidosis. Other rare findings are MCD, immunotactoid glomerulopathy, and FSGS. Immunoglobulin AL amyloidosis and cryoglobulinemic glomerulonephritis are the 2 predominant glomerular pathologies seen in patients with Waldenstrom macroglobulinemia.

Paraprotein-Mediated Kidney Diseases
MM has many renal manifestations (Table 5). Although MM is traditionally associated with tubular and glomerular disease, there are also associations of renal diseases with monoclonal gamopathy of undetermined significance, monoclonal B-cell lymphocytosis, smoldering myeloma, Waldenstrom macroglobulinemia, and low-grade lymphoma. These non-MM glomerular diseases are broadly defined as monoclonal gammapathy of renal significance (MGRS). MGRS
represents a group of disorders in which a monoclonal immunoglobulin secreted by a nonmalignant or premalignant B-cell or plasma cell clone causes kidney damage. By definition, these disorders do not meet diagnostic criteria for overt, symptomatic MM or a lymphoproliferative disorder.

The diagnosis of paraprotein-mediated diseases is challenging. Patients with paraproteinemia-associated kidney diseases typically present with AKI or hematuria/proteinuria. Serum protein electrophoresis, along with serum immunofixation and plasma FLCs, offers nearly a 100% detection rate for MM and a 96% detection rate for AL amyloidosis.177

Although circulating light chains can lead to cast nephropathy (as discussed above) and light-chain–associated proximal tubular dysfunction (Fanconi syndrome), they may also deposit in the glomeruli, leading to organized and nonorganized patterns of immunoglobulin deposits that can be seen with electron microscopy along with the clinical features of proteinuria, nephrotic syndrome, microscopic hematuria, hypertension, and deterioration of renal function. Glomerular diseases with organized deposits include AL amyloidosis, fibrillary glomerulonephritis, cryoglobulinemic glomerulonephritis, and immunotactoid glomerulonephritis. Nonorganized deposits are features of monoclonal immunoglobulin deposition disease and proliferative glomerulonephritis with monoclonal immunoglobulin deposits. TMA can also be rarely associated with monoclonal proteins.

The classification of MGRS is complex, and Table 6 describes the kidney biopsy findings, clinical presentation, associated hematologic disorders, mechanism of injury, and treatment outcomes (where available) for each type of kidney biopsy finding associated with MGRS.178–180 Once the renal pathologic diagnosis is made, the next challenge is detecting a clonal cell line responsible for the production of the monoclonal protein.

Treatment of MGRS is directed at the underlying B-cell or plasma cell clones. Data support the finding that, if a clonal cell population is eradicated, then renal outcomes are improved.181,182 For patients who present with significant fibrosis on the kidney biopsy and late-stage CKD, such as stage 4 and 5 disease and/or ESKD, chemotherapy might

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**TABLE 4. Clues Linking a Glomerular Disease With a Paraneoplastic Process**

| GLOMERULAR DISEASE PATHOLOGY | CLINICAL AND PATHOLOGY CLUES |
|------------------------------|------------------------------|
| Membranous nephropathy       | Age >65 y, smoking history, negative anti-PLA2R in the serum, negative staining on kidney biopsy for anti-PLA2R, presence of >8 inflammatory cells in the glomeruli, absence of IgG4 deposits, presence of THSD7A staining, clinically resistant to several cytotoxic agents (cyclophosphamide, rituximab, calcineurin inhibitors) |
| Minimal change disease       | Age >65 y; no other secondary cause found, such as medications or infections, clinically resistant to several cytotoxic agents (steroids, cyclophosphamide, rituximab, calcineurin inhibitors) |
| Focal segmental glomerulosclerosis | No secondary cause obviously found, clinically resistant to several cytotoxic agents (steroids, cyclophosphamide, rituximab, calcineurin inhibitors) |
| IgA nephropathy              | New diagnosis at age >65 y |
| Membranoproliferative glomerulonephritis | Monoclonal on immunofluorescence, electron microscopy shows immunotactoid or cyroglobulin-like features, no autoimmune cause found—important to screen for certain hematology malignancies, such as CLL, CML, WM, and plasma cell dyscrasias |
| ANCA vasculitis              | Clinically resistant to several cytotoxic agents (steroids, cyclophosphamide, rituximab, calcineurin inhibitors) and plasmapheresis, and no drug-induced cause found |

**TABLE 5. Paraproteinemia-Related Renal Diseases**

| Tubular disorders             | Myeloma cast nephropathy |
|                              | Interstitial nephritis   |
|                              | Infiltration of plasma cells |
|                              | Acute tubular necrosis (paraprotein or treatment related) |
|                              | Proximal tubulopathy (including Fanconi syndrome) |
| Glomerular diseases           | Monoclonal immunoglobulin (Ig) deposition disease (light chain/heavy chain) |
|                              | Amyloidosis               |
|                              | Fibrillary glomerulonephritis with monoclonal deposits |
|                              | Immunotactoid glomerulopathy |
|                              | C3 glomerulonephritis with monoclonal deposits |
|                              | Proliferative glomerulonephritis with monoclonal deposits |
|                              | Cryoglobulinemic glomerulonephritis |
|                              | Monoclonal crystalline glomerulonephritis |
|                              | Membranous-like glomerulonephropathy with masked IgG κ deposits |
|                              | Thrombotic microangiopathy (paraprotein or treatment related) |
| Electrolyte disorders         | Hypercalcemia             |
|                              | Fanconi syndrome          |
|                              | Tumor lysis syndrome      |

Abbreviations: ANCA, antineutrophilic cytoplasmic autoantibody; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; IgA, immunoglobulin A; WM, Waldenstrom macroglobulinemia.
### TABLE 6. Dysproteinemia-Associated Kidney Diseases, Incidence, Pathology, and Clinical Presentations

| KIDNEY BIOPSY DIAGNOSIS | CLINICAL PRESENTATION | PATHOLOGY | MOST COMMON PROTEIN | HEME DISORDER | CLONE DETECTION RATE, % | PARAPROTEIN DETECTION RATE, % | RENAL OUTCOMES |
|-------------------------|------------------------|-----------|---------------------|---------------|------------------------|-----------------------------|----------------|
| Cast nephropathy         | AKI, nonnephrotic proteinuria | Tubular damage—intimal obstruction, interstitial nephritis | κ | MM, CLL, SMM, WM | 100 | 100 | Excellent renal recovery with chemotherapy agents with or without plasmapheresis |
| LCPT                    | AKI, Fanconi syndrome | Tubular damage, nonnephrotic range proteinuria | κ | MM, MGUS, SMM, CLL, NHL, WM | 90-100 | 90-100 | ESKD not defined; median renal survival, 64 mo |
| Crystalglobulinemia      | AKI, proteinuria? | Tubular, and vascular damage | κ | MM, LPL | 100 | 100 | ESKD not defined; median renal survival, 135 mo |
| AL/AH amyloidosis        | Proteinuria, AKI | Glomerular and vascular deposition, Congo red-positive, 8-12 nm randomly arranged fibrils | λ, IgG (if heavy chain) and Igλ if combined | MM, CLL, LPL | 100 | 100 | Overall patient survival, 5 y; proteinuria >5 g and eGFR <50 mL/min best predictor of dialysis at 3 y |
| LCDD                    | AKI, CKD, proteinuria | Deposition of pathologic LC in the glomeruli, tubules, and vasculature | κ | MM (50%), MGUS, SMM | 90-100 | 90-100 | Renal response rate, 53% if heme response achieved; median renal survival, 5.4 y; overall survival, 67% (57% at 5 y); ESKD, 53% |
| HCDD                    | AKI, CKD, proteinuria | Deposition of truncated HC in glomeruli, tubules, and vasculature | IgG1 | MM (29%), MGUS, SMM | 100 | 100 | Renal survival, 5.5 y; overall survival, 67% at 5 y |
| LCHDD                   | AKI, CKD, proteinuria | Deposition of both heavy chain and light chain in glomeruli, tubules, and vasculature | IgG1 κ | MM (50%), MGUS, SMM | 90-100 | 90-100 | Median time to dialysis, 2-3 y; mean survival, 4-5 y |
| Cyro GN (type 1)        | AKI, HTN, RPGN | Glomerular and vascular deposition of (Congo red-negative, paired microtubules 25-40 nm) monoclonal protein | IgG/IgM with κ | MM, WM, CLL, B-NHL, MGUS, HCL | 76-82 | 90-100 | Partial or complete remission, >78% |
| Cyro-GN (type 2)        | AKI, HTN, RPGN | Glomerular and vascular deposition of (Congo red-negative, paired microtubules 25-40 nm) monoclonal protein | IgM κ | LPL, WM, B-CLPD | 40-90 | NA | Not available |
| ITG                     | Proteinuria, hematuria, CKD | Glomerular deposition of protein (Congo red-negative, 30-60 nm microtubules) | IgG1 | CLL (19%), MM, LPL | 63-71 | 63 | ESKD, 17%; remission, 50% |
| PGNMID                  | AKI, HTN, proteinuria, hematuria | Glomerular deposition of protein | IgG3 κ | Zero to some cases of MGUS, SMM | 20-30 | 30-40 | ESKD risk, 38%-100% |
| C3 GN                   | AKI, RPGN, proteinuria, HTN | Alternative pathway activation and nonmonoclonal deposits | IgG κ | MGUS, SMM, MM, CLL, lymphoma | 33-83 | 100 | ESKD risk, 56% |
| Fibrillary GN           | AKI, HTN, proteinuria | Glomerular deposition of protein (Congo red-negative, DNAJB9-negative, 15-20 nm randomly arranged fibrils) | IgG | MM, CLL | 15-17 | NA | ESKD, 44% |
| TMA                     | AKI, HTN, CKD | Direct endothelial injury | IgG | MM, SMM, MGUS | NA | NA | ESKD, 50% |

**Abbreviations:** AH amyloidosis, heavy-chain amyloidosis; AKI, acute kidney injury; AL amyloidosis, light-chain amyloidosis; B-CLPD, B-cell chronic lymphoproliferative disorder; CKD, chronic kidney disease; CLL, chronic lymphocytic leukemia; Cyro, cryoglobulinemia; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GN, glomerulonephritis; HC, heavy chain; HCDD, heavy-chain deposition disease; HCL, hairy cell leukemia; HTN, hypertension; Ig, immunoglobulin; ITG, immunotactoid glomerulopathy; LC, light chain; LCDD, light chain deposition disease; LCHDD, light-chain/heavy-chain deposition disease; LCPT, light-chain proximal tubulopathy; LPL, lymphoplasmacytic lymphoma; MGUS, monoclonal gammopathy of unclear significance; MM, multiple myeloma; NA, not applicable; NHL, non-Hodgkin lymphoma; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits; RPGN, rapidly progressive glomerulonephritis; SLL, small lymphocytic lymphoma; SMM, smoldering myeloma; TMA, thrombotic microangiopathy; WM, Waldenstrom macroglobulinemia.
not be indicated unless a kidney transplant is planned. A complete hematologic response is required before kidney transplantation to prevent recurrence because most patients with MGRS have a high risk of recurrent renal disease after kidney transplantation.178,183

Chronic Kidney Disease and the Risk of Cancer

Observational studies have suggested an increased incidence of cancer in patients with CKD.2,5,23,184-186 In addition, new and more effective therapies have increased cancer survival, and these patients may develop CKD as a direct result of their malignancy and/or its treatment. This is particularly true among elderly patients with cancer as well as those with common comorbidities, which increase the prevalence of CKD.186 Therefore, CKD is a risk factor for cancer, and cancer is a risk factor for the development of CKD.

Risk of CKD Resulting From Malignancy or Therapy Treatment

CKD is a recognized complication of cancer and its therapy. The link between cancer and CKD can be explained via several mechanisms (Fig. 10). Once CKD develops in a patient with cancer, it may limit their ability to participate in clinical trials, limit chemotherapy options for fear of toxicity and unknown dosing guidelines, and prevent the use of necessary computed tomography staging scans that require intravenous iodinated contrast.

The risk factors for developing CKD may be patient-specific, cancer-specific, or cancer-therapy-specific. The development of AKI is an important and often overlooked etiology for CKD among patients with cancer. For example, from 10% up to 73% of patients post-HSCT develop AKI, with 5% requiring renal replacement therapy and up to 60% developing CKD as a direct consequence of the AKI episode.63 Patients with severe AKI who required renal replacement therapy and who recovered were at highest risk for progression to CKD. The severity of AKI is a strong predictor of progression to CKD.187 In addition, CKD is a common complication in patients receiving antineoplastic drugs that are nephrotoxic. For example, most patients treated with cisplatin experience a small but permanent decline in eGFR. In one retrospective study of adult patients treated with cisplatin who had survived ≥5 years after the initial dose, about 1 in 3 experienced AKI, and the majority of patients who survived for at least 5 years after treatment had a permanent, small (<10 mL/minute) decline in eGFR.188 Other studies have confirmed that cisplatin-associated AKI can have a negative impact on long-term renal function and patient survival.189 Other agents, such as those targeting the VEGF pathway, can lead to TMA or FSGS, which also result in CKD.75

Another risk factor for the development of CKD includes invasive surgical procedures for the management of RCC. Postoperative AKI after radical nephrectomy is associated with a greater than 4-fold higher risk of developing new-onset CKD, and, as mentioned above, nephron-sparing partial nephrectomies are associated with improved outcomes with less postoperative AKI and CKD.190
Electrolyte Disorders in Patients With Cancer

Electrolyte disturbances may be caused by the malignancy (eg, as a paraneoplastic syndrome) or concurrent chemotherapy (eg, cisplatin).191

Hyponatremia

Hyponatremia (serum sodium <135 mEq/L) is usually related to excess total body water in relation to sodium and is a common finding in patients with cancer.192-194 It is the most common electrolyte disturbance in patients who have cancer.192 The presence of hyponatremia has been associated with shorter overall survival, a shorter time to treatment failure, and a lower disease control rate.195 Classification of hyponatremia is based on the duration of hyponatremia (acute if <48 hours, chronic if >48 hours), the volume status of the patient (hypovolemic, euvoletic, hypervolemic), and serum osmolality (hypoosmolar, isoosmolar). Hyponatremia can be present in up to 47% of hospitalized patients who have cancer, with a prevalence in most studies from 24% to 44%. Most cases result in mild hyponatremia, defined as a serum sodium level ranging from 130 to 134 mEq/L. Hyponatremia can be a subsequent cancer risk marker of occult neoplasms in other patients with undiagnosed cancer.196,197 Almost two-thirds of cases of hyponatremia in patients with cancer are present at hospital admission, and one-third are diagnosed in an outpatient setting. Common etiologies for hyponatremia in patients with cancer are listed in Table 7 and include the syndrome of inappropriate antidiuresis (SIAD), individual cancer treatments, reduced water excretion from kidney failure, decreased circulating volume (heart failure, cirrhosis, or hypoalbuminemia), and hypovolemia.198,199 SIAD is the most common etiology in patients with cancer, accounting for one-third of all cases of hyponatremia, and should be promptly recognized (see Table 8).199

Commonly, the etiology of hyponatremia in patients with cancer is multifactorial; for example, an elderly patient with small cell lung cancer may have hyponatremia from paraneoplastic SIAD, nausea, vomiting, opioid use, and concomitant diuretic use. This can complicate the assessment and evaluation of hyponatremia in patients who have cancer compared those who do not.192,193 Regardless of the etiology, hyponatremia is associated with unfavorable cancer treatment outcomes and increased length of hospital stay, and it is an independent predictor of morbidity (falls, encephalopathy, increased osteoporosis, and fracture risk) as well as mortality.195,198-201

Early clinical manifestations of hyponatremia are often nonspecific, include headache, malaise, and nausea, and can be mistaken for other common etiologies. As a result, this can delay early diagnosis of hyponatremia and its subsequent treatment. As the severity of hyponatremia increases, more prominent symptoms, such as vomiting, ataxia, confusion, respiratory arrest, and seizure, can occur and may be life-threatening.

TABLE 7. Causes of Hyponatremia in Patients With Cancer

| ETIOLOGY | MECHANISM |
|----------|-----------|
| Cancer treatment | Tubular injury |
| • Chemotherapy (vincristine, cisplatin, vinblastine, cyclophosphamide) | |
| • Hypotonic fluids/feeds | |
| Immune checkpoint treatment | Adrenalin, hypophysis, isolated ACTH deficiency |
| • Ipilimumab, nivolumab, pembrolizumab | |
| SIAD | ADH production from cancers, such as small cell lung cancer, hematologic (eg, Hodgkin disease, non-Hodgkin disease, chronic lymphatic leukemia, multiple myeloma); cancers of the head and neck, brain (primary and metastatic), skin (eg, melanoma), gastrointestinal system (esophageal, gastric, pancreatic, colon), gynecologic system, breast, prostate, and bladder; sarcoma thymoma; and adrenal malignancies |
| Insensible losses | Hypovolemia, aldosterone production |
| Appropriate ADH secretion | Nausea, vomiting, pain |
| Opioid derivatives | Increase ADH |
| Renal tubule dysfunction | Acute tubular injury (AKI, CKD) |
| Malnutrition | Low solute intake |
| Polydipsia | Infiltrating craniopharyngioma |
| Salt wasting | Cisplatin |
| Pseudohyponatremia | Production of paraproteins |

Abbreviations: ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; AKI, acute kidney injury; CKD, chronic kidney disease; SIAD, syndrome of inappropriate antidiuresis.

TABLE 8. Diagnosis of Syndrome of Inappropriate Antidiuresis

| Plasma serum osmolality <275 mOsm/kg H2O |
| Presence of euvoletic on physical examination (as defined by the absence of signs of hypovolemia or hypervolemia) |
| Elevated urinary sodium (>20-30 mEq/L or mmol/L) |
| Inappropriate urinary concentration (Uosm >100 mOsm/kg H2O) |
| Absence of other potential causes of hyponatremia, such as diuretic use, severe hypothyroidism, adrenal insufficiency |

Abbreviation: MEq/L, milliequivalents per liter.

Hyponatremia was defined as the presence of (hypotension, orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, pulmonary edema, ascites). The initial evaluation of patients with hyponatremia requires assessment of the patient’s volume status along with urine and serum osmolality, with simultaneous urine and serum sodium concentrations. Ideally, this evaluation should be sent before initiation of treatment unless there
are imminent, life-threatening symptoms (as listed above), a scenario that should be emergently managed with a 100-mL bolus of 3% sodium chloride infused intravenously over 10 minutes (repeated up to a maximum of 400 mL as needed for persistent symptoms) without hesitation (Fig. 11). In less symptomatic patients, an assessment should include key questions that will help guide treatment (Fig. 11). Therefore, treatment decisions should be centered around symptom severity as well as the duration of hyponatremia. In acute hyponatremia, defined as the onset of hyponatremia in <48 hours, rapid correction of serum sodium to normal levels can occur without the risk of complications, such as osmotic demyelination syndrome (ODS). For patients with hyponatremia duration >48 hours or if the duration is not known (chronic hyponatremia), the rate of correction should not exceed 4 to 8 mEq/L per day for those patients without risk factors for ODS. Alcoholism, malnutrition, hypokalemia, liver disease, and severe hyponatremia (defined as <110 mEq/L or mmol/L) are all considered significant risk factors for the development of ODS after correction of hyponatremia and should alert the clinician to lowering the rate of correction to no more than 4 to 6 mEq/L in 24 hours. In any scenario, a nephrology consultation should be considered for assistance in the management of moderate and severe cases of hyponatremia.

The underlying cause of the hyponatremia should be addressed. For patients with hypovolemia, intravenous hydration with isotonic fluids, such as 0.9% normal saline, should be provided. It is important to avoid hypotonic fluids as they can exacerbate the hyponatremia. For patients with hypervolemic hyponatremia, fluid and salt restriction should be instituted and may also be treated with loop diuretics as needed. For patients with SIAD, fluid restriction (500 mL/day below the 24-hour urine volume) and salt loading with either a high-sodium diet or sodium chloride tablets is an option. Predictors of the likely failure of fluid restriction in SIAD are a 24-hour urine volume <1500 mL/day, a urine osmolality of >500 mOsm/kg H₂O, the sum of the urine sodium and potassium concentrations exceeding the serum sodium concentration, and failure of serum sodium to rise by 2 mEq/L with a 1.2-L/day fluid restriction. Other treatment options for SIAD include vasopressin 2 receptor antagonists, such as tolvaptan or oral urea. There are only a few clinical studies, mostly observational studies with small patient numbers, that have assessed tolvaptan use in oncology patients with SIAD. Most studies showed that oral tolvaptan was effective and safe for patients with SIAD, and this approach allows for more liberal fluid intakes. Urea has also been shown to be effective, but tolerability and palatability may be issues.

Hypernatremia
Hypernatremia (serum sodium concentration >145 mEq/L) is also common, with a prevalence rate of 2.6%...
Hypernatremia raises the volume assessment and vital signs, urinary and serum osmolality, polyuria, and weakness, with more severe symptoms marked by hyperthermia, seizure, delirium, coma, and death. An initial evaluation for hypernatremia includes increased free water loss or inadequate water repletion. Early treatment of the collecting duct and promote solute excretion. Marked by hyperthermia, seizure, delirium, coma, and death. An initial evaluation for hypernatremia includes increased free water loss or inadequate water repletion. Early treatment of the collecting duct and promote solute excretion.

Hypernatremia typically should not exceed 0.5 mmol/L per hour, although a recent observational study did not find any evidence that more rapid correction of hypernatremia is associated with adverse events in critically ill patients.

**Hypercalcemia**

Hypercalcemia of malignancy is related to either osteolytic release of calcium from metastatic disease or from stimulation of osteoclast activity by release of tumor-derived endocrine factors. Patients with mild hypercalcemia (corrected serum calcium <12 mg/dL) may be asymptomatic or complain of nausea, vomiting, weakness, anorexia, polyuria, constipation, or depression. With more severe hypercalcemia, patients may present with volume depletion, confusion, renal failure, cardiac arrhythmias, or pancreatitis. Measurement of PTH–related peptide should be considered to identify cases of humoral hypercalcemia of malignancy (non-PTH–mediated) that can occur in squamous cell, renal cell, bladder, breast, and ovarian carcinomas and certain in lymphomas and leukemias. Serum and urine protein electrophoresis are key to identifying MM.

Medical treatment of hypercalcemia centers around aggressive volume resuscitation to promote calcium excretion. Furosemide is no longer recommended for the routine management of hypercalcemia except when volume overload exists. For patients who have ESRD with hypercalcemia, dialysis with a low-calcium dialysate along with cessation of all calcium-based medications and activated forms of vitamin D3 should be performed. Patients with severe hypercalcemia may be effectively treated with subcutaneous calcitonin and intravenous bisphosphonates. RANKL inhibitors, such as denosumab, may be considered as an alternative therapy to bisphosphonates for patients with moderate-to-severe CKD and those with ESRD. When using denosumab, it is critically important that patients have normal levels of vitamin D because, in the setting of vitamin D deficiency, the use of denosumab can lead to severe hypocalcemia. In specific circumstances, corticosteroids are useful in the treatment of hypercalcemia associated with lymphomas.

**Hypocalcemia**

Hypocalcemia is defined as corrected total blood calcium <8.5 mg/dL or ionized blood calcium <4.6 mg/dL. Although most patients are asymptomatic from hypocalcemia, some patients experience muscle cramps, confusion, numbness, and tingling in the lips and fingers. The primary cause of hypocalcemia in patients with cancer is sequestered calcium from excessive uptake by bone-forming osteoblastic metastases. Hypocalcemia can occur in approximately 30% of patients with advanced prostate cancer who have proven bone metastases. The characteristic electrocardiogram finding of hypocalcemia

**TABLE 9. Causes and Treatment of Hypernatremia**

| ETIOLOGY                                              | TREATMENT                                      |
|-------------------------------------------------------|------------------------------------------------|
| Insensible loses/inadequate intake of free watera     | Repletion with isotonic saline, followed by oral water, or 0.45% NS, or 5% dextrose to reduce hyperosmolality |
| Hypervolemia from isotonic fluid administration       | Oral water, or 0.45% NS, or 5% dextrose; loop diuretics |
| Central diabetes insipidus                           | Oral water, or 0.45% NS, or 5% dextrose; desmopressin or vasopressin |
| Nephrogenic diabetes insipidus                        | Diuretics, NSAIDsb                             |

Abbreviations: NS, normal saline; NSAID, nonsteroidal anti-inflammatory drugs.

aThe etiology of losses included diuretic use, high-output gastrointestinal losses, and neutropenic fever.

bThe etiology of central diabetes insipidus was from neurosurgery or, very rarely, from hypothalamic/pituitary or metastatic brain lesions.

Diuretics and NSAIDs were used to reduce solute delivery to the diluting segment of the collecting duct and promote solute excretion.

Similar to patients without cancer, hypernatremia is an independent risk factor for mortality. It results from increased free water loss or inadequate water repletion. Early symptoms may be notable for confusion, lethargy, irritability, polyuria, and weakness, with more severe symptoms marked by hyperthermia, seizure, delirium, coma, and death. An initial evaluation for hypernatremia includes a detailed history and physical examination, including volume assessment and vital signs, urinary and serum osmolality, and sodium levels. Hypernatremia raises the serum osmolality above 295 mOsm/kg and, when associated with high urinary osmolality (usually higher than the serum osmolality), indicates excessive free water loss and/or inadequate fluid intake. The presence of a low urinary osmolality (usually less than the serum osmolality and closer to 100 mOsm/kg) is diagnostic of nephrogenic or central diabetes insipidus and is confirmed with a water-deprivation test. However, a water-deprivation test is not needed when a random serum arginine vasopressin level is <1.0 pg/mL with the absence of a posterior pituitary bright spot on brain magnetic resonance imaging. In some cases, hypernatremia is also associated with excessive solute loss seen with azotemia, corticosteroid use, or post-AKI. Treatment is centered around therapy of the underlying etiology and the administration of oral water or hypotonic solutions, such as 0.45% saline or 5% dextrose, to reduce hyperosmolality (Table 9). The exact amount of fluids administered depends on the free water deficit and should be calculated using a free water deficit equation (% total body water [as a fraction] × weight [kg] × [current Na/ideal Na – 1]). The rate of correction of hypernatremia typically should not exceed 0.5 mmol/L per hour, although a recent observational study did not find any evidence that more rapid correction of hypernatremia is associated with adverse events in critically ill patients.
is prolongation of the QTc interval because of lengthening of the ST segment, which is directly proportional to the degree of hypocalcemia. This finding should prompt emergent treatment with an intravenous infusion of 10% calcium gluconate 2 grams over 2 hours. Treatment with intravenous calcium is also necessary when the corrected calcium is <7.5 mg/dL or if the patient has signs or symptoms of hypocalcemia.193

Hypocalcemia may also be caused by hypoparathyroidism after surgery for head and neck or thyroid cancer and may result in severe and prolonged postoperative hypocalcemia.216 These patients are often initially managed with continuous intravenous calcium infusions, with the rate of infusion adjusted depending upon subsequent calcium levels and patient symptoms. Simultaneously, enteral calcium supplements together with an activated form of vitamin D3 (calcitriol) should be provided.

**Hypokalemia**

Hypokalemia is defined as a serum potassium level <3.5 mEq/L and is common in patients who have cancer.191,193 The causes of hypokalemia are grouped into cancer-related or chemotherapy-related hypokalemia and can be broadly categorized further into 4 categories: 1) inadequate dietary potassium intake (anorexia, nausea, mucositis, surgery, or tumor-induced dysphagia/odynophagia), 2) increased extra-renal potassium losses (vomiting and diarrhea from chemotherapy use), 3) increased renal potassium losses (vomiting and diarrhea from chemotherapy use or gastrointestinal neuroendocrine tumors), 4) increased extra-renal potassium losses (vomiting and diarrhea from chemotherapy use or gastrointestinal neuroendocrine tumors).192,193 The mechanism of paraneoplastic ACTH-induced hypokalemia is through excessive cortisol secretion by the adrenal gland, which produces a significant mineralocorticoid effect and can be treated with a mineralocorticoid receptor antagonist, such as spironolactone or eplerenone.217,218 Another cancer-related cause of hypokalemia is through production of lysozyme by various leukemias, resulting in tubular injury and failure to reabsorb urinary potassium.219,220

The mainstay of treatment involves intravenous or oral potassium, an increase in dietary potassium intake, avoidance of medications known to promote potassium loss (such as diuretics), and co-correction of concurrent hypomagnesemia. Ultimate therapy requires either removal of the offending chemotherapeutic agent or treatment of the malignancy. In some cases, such as with cisplatin, some degree of potassium wasting may be permanent and require ongoing therapy.

**Hypomagnesemia**

Hypomagnesemia is commonly seen in patients with cancer and may be caused by diminished dietary intake or renal magnesium wasting. A fractional urinary excretion of magnesium >15% or a 24-hour urine magnesium level >24 mg/day suggests renal magnesium wasting. Levels below this suggest inadequate magnesium intake and/or gastrointestinal losses. Hypomagnesemia may be present in from 4.4% up to 5.4% of patients taking antiepidermal growth factor receptor (EGFR) monoclonal antibodies, such as panitumumab and cetuximab, that are used for many additional cancers other than metastatic colorectal cancer and are associated with a better progression-free survival.221 Most patients with hypomagnesemia are asymptomatic, and signs and symptoms such as weakness, muscle spasm, or ventricular arrhythmia usually do not arise until the serum magnesium concentration falls below 1.2 mg/dL.

The mechanism of hypomagnesemia may rest between the interaction of anti-EGFR monoclonal antibody with transient receptor potential cation channel, subfamily M, member 6 (TRPM6) in distal collecting tubules, preventing TRPM6 from inserting into the apical membrane of the distal tubular cells and blocking absorption of magnesium from the tubular lumen.222 It is interesting that the presence of hypomagnesemia may serve as a marker for clinical efficacy of these agents.221

**Hypophosphatemia**

Hypophosphatemia, defined by a serum phosphate level <2.5 mg/dL (0.81 mmol/L), can be induced by various causes in patients with advanced cancer, such as malnutrition (poor phosphate intake in diet), persistent diarrhea or high-output stomas after gastrointestinal diversion surgery, or chemotherapy causing renal wasting from a Fanconi syndrome or a proximal tubulopathy.223 Chemotherapeutic agents, such as ifosfamide and the tyrosine kinase inhibitors (eg, imatinib, sunitinib, sunitinib), have all been associated with hypophosphatemia.224,225 Dabrafenib, a new BRAF inhibitor for melanoma, had an incidence of hypophosphatemia in 7% of patients.226 A rare cause of hypophosphatemia in patients with cancer is tumor-induced osteomalacia, a rare paraneoplastic syndrome characterized by hypophosphatemia resulting from decreased tubular phosphate reabsorption, with a low or inappropriately normal level of active vitamin D.227 Constitutive release of fibroblast growth factor-23 (FGF-23) from primary tumors was identified as responsible for hypophosphatemia during tumor-induced osteomalacia, such as with the rare benign tumor phosphaturic mesenchymal tumor, mixed connective tissue variant, and can lead to profound hypophosphatemia, requiring surgical resection of tumor or use of a new anti-FGF-23 monoclonal antibody. Another cause of hypophosphatemia is tumor genesis
syndrome, a state of high cell-turnover states such as leukemia and lymphoma.

Type B Lactic Acidosis

Type B lactic acidosis is a rare metabolic complication of malignancy more frequently observed in hematologic malignancies such as lymphoma or leukemia, although case reports also exist in solid malignancies. The etiology of type B lactate acidosis is unclear, and many theories have been proposed. It is associated with a poor prognosis regardless of the treatment and may be invariably fatal.

Summary

The field of onconephrology is rapidly evolving, and there are many intersections between oncological care and nephrology. Through multidisciplinary and collaborative efforts between oncology and nephrology, the promise of cancer treatments can be realized while minimizing kidney-related complications that have both short-term and long-term consequences. In addition, the myriad of kidney-related complications associated with cancer require a new knowledge base, which is rapidly evolving as we learn more about how cancer can lead to kidney disease.

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