KIDNEY RESEARCH AND CLINICAL PRACTICE

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Acute kidney injury in the patient with cancer

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Dramatic advances in the care of patients with cancer have led to significant improvement in outcomes and survival. However, renal manifestations of the underlying cancer as well as the effects of anti-neoplastic therapies leave patients with significant morbidity and chronic kidney disease risks. The most common renal manifestations associated with cancer include acute kidney injury (AKI) in the setting of multiple myeloma, tumor lysis syndrome, post-hematopoietic stem cell therapy, and AKI associated with chemotherapy. Knowledge of specific risk factors, modification of risk and careful attention to rapid AKI diagnosis are critical for improving outcomes.

Keywords: Acute kidney injury, Chemotherapy, Neoplasms, Oncology

Introduction

Patients with cancer are at high risk for infections, sepsis, tumor lysis syndrome (TLS), drug-associated toxicities, and other comorbidities that significantly increase the likelihood of developing acute kidney injury (AKI) [1,2]. The development of AKI in these patients represents a significant event that increases mortality and morbidity and can limit the effectiveness and use of chemotherapeutic regimens [1,2]. Unfortunately, no effective therapies for AKI exist, making prevention critically important. Prevention of AKI rests on the recognition of patient- and cancer-specific risk factors that can be targeted for intervention to lower the likelihood of AKI.

Epidemiology

Two recent studies described an overall one-year incidence of AKI in cancer patients between 11% and 20%, with higher risks in patients with hematological cancers [3,4]. Most recently, a study from China that surveyed over 7 million patients demonstrated an incidence of AKI (defined as at least a 50% increase in baseline serum creatinine) at 14 to 20% depending upon the hospital type (community vs. academic, respectively) [5]. Some studies have noted much higher rates of AKI (60%), but are biased with a larger number of critically ill patients with hematological malignancies [6,7]. Studies support that the highest incidences of AKI occur with renal cell cancer, liver cancer, multiple myeloma, leukemia, and post-hematopoietic stem cell transplantation (HSCT) [3,4]. In a large Danish cohort of patients with cancer and AKI, 5% required renal replacement therapy (RRT) within one year of AKI onset [4]. However, studies in higher risk, critically ill populations have reported the need for RRT in 8% to 60% of patients depending on the severity of AKI and underlying comorbidities [8]. A recent study investigated the incidence of AKI in 163,071 patients receiving systemic treatment (presumably a smaller subset of patients with malignancy) [9], and identified 10,880 patients who experienced AKI. The rate of AKI was 27 per

1,000 person-years, with an overall cumulative incidence of 9.3%. Malignancies with the highest 5-year AKI incidence were myeloma (26.0%), bladder cancer (19.0%), and leukemia (15.4%). Advanced cancer stage, chronic kidney disease (CKD), and diabetes were associated with an increased risk of AKI (adjusted hazard ratios [aHR] = 1.41, 95% confidence interval [CI] = 1.28 to 1.54; aHR = 1.80, 95% CI = 1.67 to 1.93; and aHR = 1.43, 95% CI = 1.37 to 1.50, respectively). Interestingly, the annual incidence of AKI increased from 18 to 52 per 1,000 person-years between 2007 and 2014.

Risk factors associated with the development of AKI in cancer patients are both cancer-specific and patient-specific (Table 1). Knowledge of these risk factors is imperative for both prevention and early recognition of AKI. Clearly, hematological malignancies, older age and the presence of underlying CKD represent the greatest baseline risk factors that interact with specific types of chemotherapy to determine the overall AKI risk. This effect is modified by the occurrence of complications such as sepsis, which may significantly increase AKI risk.

AKI in cancer patients has numerous deleterious consequences, including increased mortality (especially for those with higher AKI stages, post-HSCT or requiring RRT), increased the length of hospital stay, and in one study, a lower rate of complete cancer remission [7,10–15]. In patients undergoing myeloablative conditioning regimens as part of stem cell transplants, those patients with AKI had worse overall survival and progression-free survival as well as increased risk for CKD development [16]. As another example, Libório and colleagues [15] found that mortality was 13.6% in those without AKI, and progressively increased with higher RIFLE (Risk, Injury, Failure, Loss, End stage renal disease) stage AKI (Risk, 49%; Injury, 62.3%; Failure, 86.8%). Salahudeen et al [3] also demonstrated a decrease in survival in cancer patients with AKI. Using modified RIFLE criteria, 12% of patients admitted to the hospital had AKI, with rates in the Risk, Injury, and Failure categories of 68%, 21%, and 11%, respectively. Dialysis was required in 4% of patients. In a multivariate model, the odds ratio (OR) for developing AKI was significantly higher for patients with diabetes (OR, 1.89; 95% CI, 1.51–2.36), receiving chemotherapy (OR, 1.61; 95% CI, 1.26–2.05), receiving intravenous contrast (OR, 4.55; 95% CI, 3.51–5.89), and antibiotics (OR, 1.52; 95% CI, 1.15–2.02). In patients with AKI, length of stay (100%), cost (106%), and odds for mortality (4.7-fold) were significantly greater. In addition, AKI in patients with newly diagnosed hematological malignancies was associated with a lower 6-month complete remission rate (39.4% in patients with AKI vs. 68.3% in patients without AKI) and 14.6% of patients with AKI received suboptimal chemotherapy [10]. Thus, the development of AKI can negatively impact current or future chemotherapeutic regimens, as well as potentially increase the toxicity or alter the pharmacokinetics and pharmacodynamics of these drugs. Furthermore, AKI would exclude patients from potentially beneficial clinical trials.

The long-term consequences of AKI in the patient with cancer are highly variable and it is likely that overall severity of illness, age, and functional status contributes significantly to prognosis in these patients. Thus, while some studies report poor 30-day survival in patients with AKI and cancer, other studies have not found a difference [17]. While the impact of AKI on long-term kidney function has been rarely reported in this subset of patients, this outcome also appears to be variable. One study reported that 82% of critically ill cancer patients with AKI completely recovered kidney function, while partial recovery was observed in 12%, and chronic RRT was required in only 6% of patients [11]. Other studies have reported long-term dialysis dependence in 12.9 to 23% of patients with hematological malignancies who develop dialysis-requiring AKI [6,14]. These data highlight the importance of careful and individualized decision mak-

Table 1. Risk factors and etiologies of acute kidney injury in critically ill patients with cancer

Patient-specific risk factors	Cancer-related risk factors
Age > 65 yr	Neutropenia and resulting sepsis
Underlying CKD	Post-nephrectomy for RCC
Diabetes mellitus	Hematological cancers
Potential nephrotoxin medications	Urinary tract obstruction
(NSAIDs, ACEi, ARBs)	Post-HSCT
Comorbid conditions	Thrombotic microangiopathy
(such as cirrhosis, heart	Tumor lysis syndrome
failure, nephrotic syndrome)	Hypercalcemia
	Paraneoplastic glomerular diseases
	Chemotherapy toxicities

Individual risk for acute kidney injury is due to a combination of host and cancer-related factors.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; HSCT, hematopoietic stem cell transplant; NSAIDs, non-steroidal anti-inflammatory drugs; RCC, renal cell cancer.

ing in patients with AKI, as some patients will have good outcomes.

AKI in hematological malignancies

Patients with hematological malignancies (including leukemia, lymphoma, and multiple myeloma) are at the highest risk for AKI development in most case series. AKI may be due to the direct effects of the malignancy, such as with the development of light chain cast nephropathy in patients with multiple myeloma, or may be due to downstream effects of therapy, such as with sepsis associated with immunosuppression and neutropenia [18]. Many AKI etiologies in the setting of hematological malignancies are rare, and a kidney biopsy may be required for accurate diagnosis (Table 2). A thorough diagnostic process should be undertaken in patients with AKI and hematological cancers, including urinalysis with quantification of urine protein excretion (albumin, protein electrophoresis, and total protein), free light chain (FLC) quantification, serum chemistries, complete blood counts, and renal ultrasound.

A particularly insidious cause of AKI is tumor cell infiltration of the kidneys, which is most common with lymphoma and leukemia. In these cases, renal ultrasound findings of bilaterally enlarged kidneys should prompt consideration of leukemic or lymphomatous infiltration. AKI likely results from tumor cells that cause tubular compression and disruption of the renal microcircula-

tion [19–21]. AKI in these cases is often rapidly reversible with appropriate and effective chemotherapy. However, these patients are at risk for TLS and should be managed aggressively to prevent this complication (see below).

The findings of proteinuria, microscopic hematuria, or red blood cell casts should prompt consideration of cancer-related glomerulonephritis such as membranoproliferative glomerulonephritis or amyloidosis [2]. In these cases, a kidney biopsy is critical in defining diagnosis and prognosis, along with outlining appropriate treatment. While relatively rare, malignancy-related glomerulonephritis may be the first manifestation of cancer. Thus, age-appropriate cancer screening should be performed in patients with this new diagnosis [22].

Lysozymuria (the presence of large amounts of the enzyme lysozyme in the urine) is an uncommon disorder seen in patients with acute promyelocytic, monocytic leukemia, or chronic myelomonocytic leukemia where malignant cells produce large amounts of lysozyme [23]. Lysozyme is filtered at the glomerulus and taken up by proximal tubular cells, leading to cellular damage and AKI. Urine protein electrophoresis (UPEP) can demonstrate large quantities of lysozyme in these cases. In addition, electrolyte abnormalities such as refractory hypokalemia may also be present.

Patients with multiple myeloma represent an important subclass of patients with hematological malignancies that are prone to develop AKI. The etiologies of AKI in these patients are protean and diverse (Table 3). AKI is quite common, complicating the course of myeloma in up to 20% to 50% of cases [24,25]. The most common cause of AKI in multiple myeloma is cast nephropathy. The updated 2014 criteria of the International Myeloma Working Group consider AKI by light chain cast nephropathy as a myeloma defining event [26]. Light chain cast nephropathy can rarely be associated with other hematological cancers such as Waldenstrom macroglobulinemia,

Table 2. Etiologies of acute kidney injury in patients with hematological malignancies

General non-specific etiologies	Tumor-related etiologies
Volume depletion secondary to nausea, vomiting, diarrhea	Tumor (leukemia or lymphoma) infiltration of the kidney
Sepsis	Obstructive nephropathy due to retroperitoneal lymphadenopathy (lymphoma)
Iodinated contrast nephrotoxicity	Lysozymuria in chronic myelomonocytic leukemia and acute monocytic leukemia
	Disseminated intravascular coagulation
	Tumor lysis syndrome
	Hypercalcemia
	Glomerular diseases
	Myeloma-specific etiologies such as cast nephropathy
	Chemotherapy-related nephrotoxicity

Table 3. Etiologies of acute kidney injury in patients with multiple myeloma

Paraprotein-related	Metabolic disturbances
Light chain cast nephropathy	Hypercalcemia secondary to bone involvement
Light chain related proximal tubular injury with or without Fanconi syndrome	Hyperuricemia with large tumor burden
Light chain deposition disease	
Amyloidosis (more common with lambda light chains)	

chronic lymphocytic leukemia, or lymphoma [27].

Light chain cast nephropathy develops when FLCs, which are freely filtered by the glomerulus, bind to Tamm-Horsfall protein (uromodulin) in the thick ascending limb of the loop of Henle to form insoluble casts that obstruct the tubular lumen and lead to local inflammation [28,29]. There are common binding sites on kappa and lambda light chains which interact in a noncovalent manner with carbohydrate moieties on Tamm-Horsfall proteins [30]. These interactions and the formation of obstructing casts are promoted in the setting of reduced tubular flow rates as well as when the concentrations of urinary electrolytes (sodium and chloride) are higher (such as with diuretic use) [31]. There is also a direct relationship between the risk of cast nephropathy and the serum concentration of FLCs [32]. Histological examination reveals diffuse interstitial inflammation, which may be triggered by leakage of light chains into the kidney interstitium. This leads to activation of multiple pro-inflammatory pathways, and on-going inflammation may progress to irreversible kidney injury, highlighting the importance of early and aggressive therapy [33].

The diagnosis of cast nephropathy centers on measurement of serum FLCs with quantitative measurement of kappa and lambda FLCs as well as serum protein electrophoresis (SPEP) and UPEP [34,35]. Serum FLCs and SPEP identify the presence of pathogenic FLC, and UPEP helps to distinguish paraprotein-related glomerular diseases characterized by albuminuria from cast nephropathy, where proteinuria is largely non-albumin FLCs [36]. A study from the Mayo Clinic demonstrated that in patients with light chain cast nephropathy, urine albumin excretion was less than 25% of total urine protein excretion, with a median of 7% [37]. Higher levels of urine albumin excretion should prompt consideration of kidney biopsy. In addition, the International Myeloma Working Group recommends a kidney biopsy to determine alternative causes of AKI if serum FLC levels are less than 500 mg/L (or 50 mg/dL) [26].

Treatment of cast nephropathy has evolved considerably in the last decade and centers on provision of adequate hydration to augment tubular flow and treat pre-existing volume depletion ("flushing out the tubular casts"), along with chemotherapy to rapidly reduce FLC levels. Obviously, any potentially nephrotoxic medications should be stopped and avoided. Effective chemo-

therapy regimens include proteasome inhibitors such as bortezomib along with other agents such as thalidomide, corticosteroids, vincristine, and adriamycin in various combinations [38–41]. These regimens have been associated with high rates of improvement in renal function as well as significantly improved survival [38–41]. Importantly, bortezomib has the added benefit of acting quickly to improve glomerular filtration rate (GFR) with a median time of response at 1.34 months [42]. The addition of the alkylating agent bendamustine to a regimen of prednisone and bortezomib has also increased renal response rates to greater than 80%, with the majority of the response occurring within 6 weeks [43].

Given that a rapid reduction in the serum concentration of FLCs is critical for improving kidney function, there is continued interest in the use of extracorporeal therapies to rapidly remove FLC while more definitive chemotherapy is being implemented. Thus, the use of therapeutic plasma exchange (TPE) or high-cutoff hemodialysis (using large pore dialysis membranes to facilitate FLC removal) remains of great interest and also of great controversy. In terms of plasmapheresis, the randomized controlled trials have been small (the largest included 97 patients) and inconclusive [44]. Most recently, the use of high flux dialyzers with greater capacity for light chain removal has been studied, and two recent trials have been reported. In the European trial of FLC removal by extended hemodialysis (EuLITE), there was no benefit noted with a high flux dialyzer over conventional therapy [45]. However, high flux dialysis was found to be beneficial in the MYRE trial, which enrolled patients with biopsy-proven cast nephropathy [46]. In this trial, dialysis independence increased to 56.5% in the high flux dialysis arm, compared to 35.4% in the conventional arm ($P = 0.04$). Thus, it remains unclear if high-cutoff hemodialysis provides benefit with conflicting evidence in the two trials [47].

Hematopoietic stem cell transplantation

HSCT is an important and possibly curative treatment for cancer patients, especially those with hematological malignancies. However, AKI may complicate HSCT as a result of conditioning chemotherapy, radiation exposure, sepsis, sinusoidal obstruction syndrome (SOS), thrombotic microangiopathy (TMA), graft-versus-host disease

(GVHD), or nephrotoxic medications [48,49]. The incidence of HSCT-associated AKI ranges from 15% to 73% depending on whether an allogenic or autologous transplant is performed and high-dose or reduced intensity chemotherapeutic conditioning regimens are employed [48]. Myeloablative regimens and allogenic HSCT are associated with a higher rate of AKI [50–52]. The need for RRT develops in ~5% of patients but approaches 30% in high-risk patients [52–55]. When AKI occurs in this setting, it is associated with an increase in mortality rate, especially when it occurs early in the post-HSCT course, prior to engraftment [56]. Post-HSCT AKI is challenging to treat, as it commonly occurs in patients who are severely immunocompromised and may be manifesting other complications such as GVHD, sepsis, and other critical illnesses. Of great importance is the link between the occurrence of AKI post-HSCT and the eventual development of CKD. Hingorani [57] reported that the cumulative incidence of CKD varies between 7% and 48% and develops between 6 months and 10 years after HSCT. Risk factors for CKD include prior AKI, acute and chronic GVHD, older age at HSCT, a decrease in the GFR at baseline, hypertension, the use of calcineurin inhibitors, and exposure to total-body irradiation.

Development of HSCT-associated AKI occurs due to a number of insults, some of which are specific to this clinical scenario and others that are more general, such as sepsis. Liver injury during HSCT (especially during the conditioning regimen) may lead to hepatic SOS, which is an independent risk factor for AKI [58]. The mean incidence of SOS is 13.7% but is significantly decreasing with newer regimens [58]. Hepatic sinusoidal obstruction occurs due to sinusoidal endothelial cell and hepatocyte damage induced by cytoreductive regimens [58–60]. Hepatic SOS is characterized by painful hepatomegaly, jaundice, oliguria, and ascites and mimics hepatorenal syndrome. Hypervolemia in these cases is usually diuretic resistant, and spontaneous recovery is rare. AKI adversely affects survival, with mortality approaching 80% in those who require RRT. Prevention and treatment include infusions of prostaglandin-E, pentoxifylline, and low-dose heparin [60–62]. Early administration of defibrotide, an antithrombotic and fibrinolytic agent, appears to beneficial, and if instituted early, may lead to improvements in GFR [63,64].

In HSCT-associated TMA, patients may develop AKI or eventually CKD [65,66]. The lesion is characterized by endothelial swelling and damage, with fibrin thrombi within capillary loops and arterioles [67,68]. The conditioning regimens for HSCT can induce renal endothelial injury with subsequent TMA. GVHD may also contribute to TMA due to direct endothelial cell injury as well as from calcineurin inhibitor use [69,70]. Treatment includes discontinuing/reducing calcineurin inhibitor dose, TPE, and defibrotide [71–75]. Reported response rates for TPE range between 27% and 80% [76–81], and 64% for TPE plus cyclosporine withdrawal [78]. Rituximab may be beneficial for TMA post-HSCT, but more data is needed for this strategy [71,82–86].

Acute GVHD is another significant risk factor for the development of AKI in HSCT recipients [87]. GVHD causes AKI through cytokine-mediated renal inflammation or from cyclosporine exposure. Other AKI etiologies in patients with GVHD include vomiting and diarrhea, which can promote prerenal AKI, as well as viral reactivation (cytomegalovirus). In addition to supportive measures, treatment of GVHD includes use of prednisone, antithymocyte globulin, sirolimus, and mycophenolate mofetil [88].

Tumor lysis syndrome

TLS is a medical emergency and a common cause of cancer-induced AKI [89]. Risk factors for the development of TLS include highly chemosensitive malignancies such as lymphomas and leukemias, large tumor burden, effective cytolytic chemotherapeutic agents, elevated lactate dehydrogenase levels (> 1,500 IU), and underlying kidney disease [90,91]. The most common malignancies associated with TLS include non-Hodgkin's lymphoma, acute myeloid leukemia, acute lymphocytic leukemia, and various solid tumors [92]. The in-hospital mortality associated with TLS can approach 21%, and nearly 70% of patients experience a severe complication such as sepsis, dialysis, acute respiratory failure, mechanical ventilation, cardiac arrest, or seizures [92]. The median hospital length of stay for patients with TLS is 10 days, but this increases to 21 days if dialysis is required [92].

TLS is characterized by the release of cellular contents from tumor cells that are either spontaneously dying or killed by chemotherapy. These cellular contents can lead to hyperuricemia, hyperkalemia, hyperphosphatemia,

and hypocalcemia. While there are no universally accepted diagnostic criteria for TLS, the Cairo—Bishop definition of both laboratory and clinical criteria are commonly utilized [93]. Laboratory criteria include the following: hyperuricemia (> 8 mg/dL or a 25% increase from baseline), hyperkalemia (> 6 mmol/L or 25% increase from baseline), hyperphosphatemia (> 4.5 mg/dL or 25% increase from baseline) and hypocalcemia (< 7 mg/dL or a 25% decrease from baseline). Laboratory criteria for TLS require the presence of 2 or more of these abnormalities occurring 3 days before or 7 days after therapy. Clinical criteria include serum creatinine elevation > 1.5 times the upper limit of normal, cardiac arrhythmias, sudden death, and seizures.

AKI in TLS occurs due to a combination of cytokine release with inflammatory tubular injury, acute uric acid/xanthine nephropathy, and acute nephrocalcinosis due to an elevated calcium-phosphate product [2]. Uric acid, calcium-phosphate, and/or xanthine crystals can lead to tubular obstruction and tubulointerstitial inflammation. Hyperuricemia can also contribute to AKI through renal vasoconstriction, reactive oxygen species generation, and inflammatory cytokine release [2,94].

Diagnosis of AKI attributable to TLS requires an increase in serum creatinine along with fulfillment of laboratory criteria for TLS [89]. AKI typically develops 24 hours or later after initiation of chemotherapy. The clinical presentation depends on the combination and severity of biochemical abnormalities. For instance, if the potassium level rises high enough, patients may experience muscle weakness or cardiac arrhythmias.

Occasionally, cases of spontaneous TLS are seen. Patients with hyperuricemia (uric acid ≥ 8 mg/dL) in the presence of suspected malignancy with elevated lactate dehydrogenase (> 2 × upper limit of normal), acute oliguric or anuric kidney injury despite adequate volume resuscitation without evidence of post-obstructive cause, and urinary uric acid to creatinine ratio greater than 1.0 should be considered to have spontaneous TLS until proven otherwise. Diagnostically, uric acid crystals free or within casts may be seen on urine sediment examination.

Prophylaxis against TLS is recommended for all patients with hematological malignancies undergoing chemotherapy. Prophylaxis is also recommended for all high and moderate risk patients such as those with large tumor burdens, reduced GFR, and highly chemosensitive tumors. However, the exact regimen for prophylaxis should be tailored to the clinical circumstances and includes a combination of decreasing uric acid levels, ensuring adequate hydration and tubular urine flow rate, and management of abnormal electrolyte levels. Prevention and treatment of TLS complications include administration of intravenous fluids (~3 L/day) and xanthine oxidase inhibition (allopurinol or febuxostat) in high-risk patients prior to chemotherapy [90,91,94]. Hydration decreases extracellular uric acid, phosphorus and potassium concentrations, enhances renal blood flow and maintains GFR, which aids in maintenance of normal electrolyte levels. Ideally, intravenous hydration is started 24 to 48 hours pre-therapy.

It is also important to monitor for volume overload and use diuretics only when indicated.

Allopurinol is an isomer of hypoxanthine and inhibits the enzyme xanthine oxidase, thereby reducing uric acid synthesis. Allopurinol will increase plasma concentrations of the uric acid precursors hypoxanthine and xanthine, which can form crystals and deposit in the kidney in the presence of an alkaline urine, leading to xanthine nephropathy.

Side effects of allopurinol include fever, rash, eosinophilia, systemic hypersensitivity reactions, Stevens—Johnson syndrome, hepatitis, acute interstitial nephritis (AIN), and bone marrow suppression. Allopurinol should be started 2 to 3 days prior to therapy and continued for 10 to 14 days. It is important to realize that xanthine oxidase inhibitors will prevent *de-novo* elevations in uric acid levels but will not lower pre-existing high uric acid levels. Febuxostat is a non-purine analogue xanthine oxidase inhibitor and is useful in patients that are intolerant to allopurinol. One recent trial demonstrated that febuxostat was superior in lowering uric acid levels but there was no difference in clinical outcomes vs. allopurinol [95]. Febuxostat dosing should be 40 mg daily in patients with severe kidney function impairment.

In patients with hyperuricemia present at diagnosis as well as underlying AKI or CKD, recombinant urate oxidase (rasburicase) may be employed to correct hyperuricemia. Rasburicase catalyzes uric acid formation to soluble allantoin, which is rapidly excreted by the kidney. The drug has a rapid onset (within 4 hours) and leads to dramatic falls in serum uric acid levels. Rasburicase is

indicated for a single course of treatment for the management of plasma uric acid levels in pediatric and adult patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and elevation of plasma uric acid. Rasburicase generates hydrogen peroxide in the conversion of uric acid to allantoin and thus is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency [96–98].

The need for hemodialysis to treat TLS has likely declined since the advent of rasburicase. However, hemodialysis remains a highly effective therapy that can be used to gain control of electrolyte and acid-base issues, especially in the presence of oliguric AKI. Continuous renal replacement therapies can be utilized in the treatment of TLS and have the advantage of avoiding "rebound" metabolic disturbances. If a continuous renal replacement is utilized, higher clearance levels (at least 30–40 mL/kg/hour) should be targeted.

Hypercalcemia-induced AKI

Hypercalcemia occurs in approximately 20% to 30% of all malignancies (especially, multiple myeloma and squamous cell carcinomas) and is a common cause of AKI [99,100]. In some scenarios, such as with multiple myeloma, the presence of hypercalcemia may potentiate other AKI etiologies. Hypercalcemia promotes direct afferent arteriolar vasoconstriction and also leads to volume depletion from excessive renal sodium and water loss [101]. Hypercalcemia causes sodium wasting at the loop of Henle by activating the calcium-sensing receptor, and also leads to renal water losses by blocking arginine vasopressin activity in the distal nephrons [2]. Rarely, severe hypercalcemia may cause AKI via intratubular calcium-phosphate deposition (nephrocalcinosis), especially if the calcium-phosphate concentration product is higher than 70 mg^2/dL^2. Of note, nephrocalcinosis-associated AKI may not improve with treatment of hypercalcemia; depending upon the duration of hypercalcemia, patients may be left with significant CKD. This highlights the need for rapid lowering of serum calcium levels.

Patients often present clinically with weakness, dizziness, nausea, and polyuria along with hypotension, dry mucous membranes, and flat neck veins. Treatment of AKI centers around intravascular volume resuscitation to improve renal perfusion and GFR. This enhances calcium excretion and corrects hypercalcemia [99]. In addition to aggressive intravenous fluids with normal saline (without diuretics unless hypervolemia is present), low dose pamidronate (typically 60 mg or lower) infused over 4 hours will also lower serum calcium over a period of several days and has a longer lasting effect to prevent recurrent hypercalcemia [99,102]. Denosumab, a humanized monoclonal antibody against receptor activator of nuclear factor-κB (RANK) ligand, is also effective and does not require dose adjustment for GFR [103,104]. Rarely, dialysis may be required in the setting of severe hypercalcemia and AKI [99,105]. This is especially true if the calcium-phosphate concentration product is very high.

Drug-induced AKI

Drug-induced AKI occurs primarily from acute tubular injury (ATI), AIN, and a variety of glomerular and vascular injuries [106–110]. Given the explosion of novel agents to treat cancer, it is imperative that nephrologists stay up to date with the toxicities of these drugs. Broadly, chemotherapy-associated AKI can be separated into 3 drug classes: 1) conventional chemotherapy, 2) targeted therapies, and 3) novel immunotherapies [106–114].

Conventional chemotherapy

Conventional chemotherapeutic agents may injure all compartments of the kidney (tubules, interstitium, vasculature, and glomerulus) and thus lead to various forms of AKI. TMA is a particularly aggressive form of TMA that may lead to irreversible AKI and the need for dialysis. TMA complicates therapy with gemcitabine, mitomycin C, and cisplatin [106,107,109,114–117]. Drug-induced endothelial injury with release of von Willibrand factor multimers and plasminogen activator inhibitor, as well as exposure of a denuded endothelial surface to fibrin and platelets, facilitates the process within the renal microvasculature [106,107,109,115–117]. While drug discontinuation is required, therapy with several modalities has been disappointing. TPE is generally ineffective but may be attempted, and eculizumab as well as rituximab have only been rarely reported in case series [115–117].

Glomerular injury, specifically podocyte injury with the histological subtypes of focal segmental glomerulo-

sclerosis (FSGS) or minimal change disease, has been described with pamidronate and, rarely, zoledronate [118,119]. In most of these cases, the onset of kidney dysfunction occurs over a more extended period of time and is associated with significant proteinuria.

Several drugs cause AKI due to ATI, which is the most common lesion associated with AKI from conventional chemotherapy [106,107,109]. The platinum agents (cis- and carboplatin), ifosfamide, pemetrexed, zoledronate, and other agents damage the tubular epithelium via direct cellular toxicity, activation of apoptosis, generation of reactive oxygen species and oxidative stress, and mitochondrial injury [106,107,109]. Although drug discontinuation and supportive care improve kidney function, CKD may be a complication. In general, the risk of resulting CKD increases with both the severity and duration of AKI.

Methotrexate is associated with crystalline-induced AKI [106,107,109,120]. In this setting, intratubular crystal precipitation with obstructive and inflammatory interstitial injury promotes AKI. While intravenous fluids and urinary alkalinization are used for prevention and treatment, hemodialysis and glucarbidase may be required for severe toxicity [121,122]. Renal clearance of methotrexate is of critical importance. In the setting of AKI, toxic levels of methotrexate may accumulate, leading to severe bone marrow toxicity. Thus, AKI associated with methotrexate is a medical emergency and clinicians should monitor GFR closely in these situations and consider early use of hemodialysis or glucarbidase if methotrexate levels rise. Finally, a number of chemotherapeutic agents including carboplatin, ifosfamide, and adriamycin may cause AKI due to interstitial nephritis [106,107,109,123].

Targeted agents

This class of drugs consists of agents designed to target specific gene mutations that categorize particular cancers, thereby inhibiting oncogenic signaling cascades associated with tumor growth [108,111,124−127]. These drugs have been very successful in effectively treating cancer, but unfortunately are also associated with AKI, proteinuria, hypertension, and electrolyte disturbances [108,111,124−127]. In many cases, this is due to the fact that the pathways involved in oncogenesis may have overlapping functions in the kidney.

Anti-angiogenesis drugs (such as bevacizumab, axitinitib, sorafenib, and sunitinib) that target vascular endothelial growth factor (VEGF) cause AKI primarily via renal TMA, although FSGS and AIN have also been observed along with severe hypertension [108,124,125]. Dose-related AKI is noted with serine/threonine kinase BRAF inhibitors (vemurafenib and dabrafenib) [111,126]. Acute tubulointerstitial injury presumably occurs due to inhibition of the mitogen-activated protein kinase pathway; however, limited histological data is available [111,126]. Drug discontinuation is associated with AKI reversal in a majority of cases. Crizotinib, an anaplastic lymphoma kinase inhibitor, causes AKI via tubulointerstitial injury that is partially reversible with drug discontinuation [112,127]. This is an evolving area and clinicians should remain suspicious of drug toxicity in any patient with unexplained AKI, and kidney biopsy should be considered.

Novel immunotherapies

Immunotherapies are an important addition to cancer therapy [128−133]. Older agents such as interferon (IFN) and high-dose interleukin (IL)-2 are well-known causes of AKI [128,129]. IFN-associated AKI often presents clinically with high-grade proteinuria from FSGS or minimal change disease [129]. Direct binding of IFN to podocyte receptors and alteration of normal cellular proliferation may promote podocyte injury, although the cytokines IL-6 and -13 may also play a role [128]. Drug discontinuation (+/− steroids) may reverse AKI and proteinuria with minimal change disease, but is less effective in FSGS.

Immune checkpoint inhibitors (ipilimumab, nivolumab, and pembrolizumab) enhance tumor killing by preventing dendritic cells and tumor antigen ligand binding to cytotoxic T-lymphocyte-associated protein (CTLA)-4 and programmed death (PD-1) receptors, respectively [113,114,130]. This activates and further increases T-cell killing of tumor cells. Unfortunately, loss of tolerance to self and perhaps exogenous medications that have a predisposition to lead to an immune reaction, leads to AIN and a variety of glomerular lesions [113,114,130]. Drug discontinuation plus steroids is generally effective in reversing AKI, especially if treatment is started early, but a significant number of patients are left with CKD. However, it is critically important to realize that AKI in the setting of immune checkpoint inhibitors may be associated

with tubular or glomerular injury and thus, kidney biopsy should be considered.

Chimeric antigen receptor (CAR) T-cells are host cells that are harvested and engineered to express receptors that recognize and bind tumor antigens [131]. T-cells directly target and destroy cancer cells. However, this process promotes macrophage activation and cytokine release syndrome, which can result in capillary leak and prerenal AKI [132,133]. TLS may also develop and risks AKI [132,133]. Prevention and treatment of AKI include pretreatment chemotherapy to reduce the tumor burden and steroids [132,133]. In the setting of severe cytokine release syndrome, an IL-6 receptor blocker and/or steroids may reduce adverse effects [132,133].

Summary

Dramatic advances in the care of patients with cancer have occurred in a short period of time and have led to demonstrable increases in longevity. However, a consequence of these advanced therapies has been the occurrence of AKI in many forms. Rapid recognition of AKI as well as appropriate therapy is critical to sustain the gains in outcomes associated with novel chemotherapeutics. Increasingly, AKI etiologies in patients with cancer have become more complex and multi-factorial (for example, chemotherapy-induced AKI exacerbated by the development of sepsis in a patient with neutropenia). Clinicians should think broadly about the many possible AKI etiologies and, in uncertain cases, kidney biopsy should be considered. Lastly, when possible, there should be a focus on AKI prevention, as AKI has the potential to significantly worsen outcomes and limit available therapies for cancer treatment.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors' contributions

Mitchell H. Rosner and Mark A. Perazella contributed equallly to the preparation of the manuscript.

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