

Acute Kidney Injury in Critically Ill Patients with Cancer

Shruti Gupta¹, Prakash Gudsoorkar,² and Kenar D. Jhaveri³

Abstract

Advances in cancer therapy have significantly improved overall patient survival; however, AKI remains a common complication in patients with cancer, occurring in anywhere from 11% to 22% of patients, depending on patient-related or cancer-specific factors. Critically ill patients with cancer as well as patients with certain malignancies (e.g., leukemias, lymphomas, multiple myeloma, and renal cell carcinoma) are at highest risk of developing AKI. AKI may be a consequence of the underlying malignancy itself or from the wide array of therapies used to treat it. Cancer-associated AKI can affect virtually every compartment of the nephron and can present as subclinical AKI or as overt acute tubular injury, tubulointerstitial nephritis, or thrombotic microangiopathy, among others. AKI can have major repercussions for patients with cancer, potentially jeopardizing further eligibility for therapy and leading to greater morbidity and mortality. This review highlights the epidemiology of AKI in critically ill patients with cancer, risk factors for AKI, and common pathologies associated with certain cancer therapies, as well as the management of AKI in different clinical scenarios. It highlights gaps in our knowledge of AKI in patients with cancer, including the lack of validated biomarkers, as well as evidence-based therapies to prevent AKI and its deleterious consequences.

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Introduction

The field of hematology/oncology has made great strides toward treating cancer; however, AKI remains a common complication, occurring in 9% of patients initiating systemic therapy (1). Malignancies associated with the highest 5-year risk of AKI include multiple myeloma (26%), bladder cancer (19%), and leukemia (15%) (1). Other studies have found a high risk of AKI among patients with urogenital cancers and liver cancer (2). Additional high-risk populations include critically ill patients with cancer admitted to the intensive care unit (ICU) as well as those who have undergone hematopoietic stem cell transplant (HSCT) (3,4). The spectrum of AKI is broad (Figure 1) and is driven by cancer-related, patient-specific, and treatment-related factors. Noncancer-related risk factors for AKI include advanced age, CKD, diabetes, and concomitant administration of diuretics and renin-angiotensin receptor blockers (1), antibiotics, or intravenous contrast (5). AKI can have devastating consequences, including higher costs of hospitalization (6), lower rates of cancer remission (7), and even higher mortality (8). Early recognition and prevention are, therefore, critical to minimize the consequences of AKI.

Cancer-Associated AKI

Monoclonal Gammopathies and AKI

AKI commonly occurs in the setting of monoclonal gammopathies and results from the abnormal deposition or activity of a paraprotein in the kidney. Multiple myeloma is the most common malignant monoclonal

gammopathy and is associated with AKI in up to half of cases (9). Patients with multiple myeloma and kidney impairment have higher mortality compared with those without kidney involvement (10). Cast nephropathy is a myeloma-defining event and occurs when an excess of free light chains binds with uromodulin glycoproteins in the ascending loop of Henle, forming obstructing casts and initiating an inflammatory cascade (11). The diagnosis of cast nephropathy relies on the measurement of serum free light chains, with quantitative measurement of κ - and λ -free light chains, as well as serum and urine protein electrophoresis. The treatment of cast nephropathy has seen a paradigm shift over the past decade with the advent of clone-directed therapy, which causes apoptosis of malignant plasma cells and inhibits NF- κ B pathways that are implicated in interstitial inflammation and subsequent fibrosis (12). Extracorporeal therapy has been used to enhance the removal of free light chains, but its use remains controversial. Multiple small studies have shown no mortality benefit for therapeutic plasma exchange (13–15). Two trials examined the utility of high-cutoff hemodialysis for light chain removal; the European Trial of Free Light Chain Removal by Extended Hemodialysis in Cast Nephropathy found no difference in major clinical outcomes among patients who did and did not receive high-cutoff hemodialysis, whereas the Multiple Myeloma and Renal Failure due to Myeloma Cast Nephropathy trial demonstrated a possible reduction in dialysis dependence at 12 months among patients who received high-cutoff hemodialysis (16,17). High-cutoff hemodialysis is not recommended

¹Division of Renal Medicine, Brigham and Women's Hospital, Boston, Massachusetts

²Division of Nephrology & Kidney Clinical Advancement, Research & Education Program, University of Cincinnati, Cincinnati, Ohio

³Division of Kidney Diseases and Hypertension, Donald and Barbara Zucker School of Medicine, Great Neck, New York

Correspondence:

Dr. Shruti Gupta, Division of Renal Medicine, Brigham and Women's Hospital, 75 Francis Street, MRB-4, Boston MA 02115, or Dr. Kenar D. Jhaveri, Division of Kidney Diseases and Hypertension, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, Hempstead, NY. Email: sgupta21@bwh.harvard.edu or kjhaveri@northwell.edu

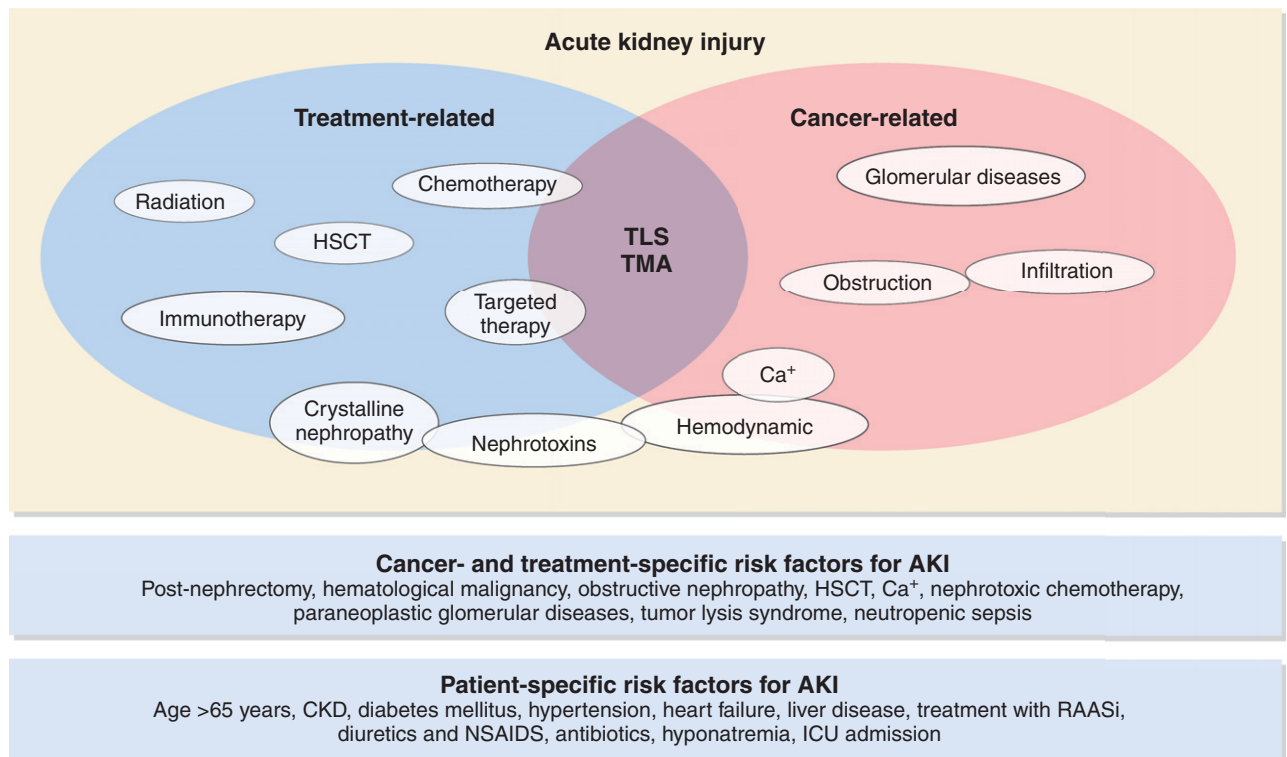


Figure 1. | The spectrum of AKI is broad in patients with cancer. Ca⁺, hypercalcemia; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit; NSAID, nonsteroidal anti-inflammatory agent; RAASi, renin-angiotensin-aldosterone system inhibitor; TLS, tumor lysis syndrome; TMA, thrombotic microangiopathy. Adapted from ref. 137, with permission.

on the basis of available data, and its availability is limited in the United States. Plasmapheresis has also been studied among patients with a new diagnosis of multiple myeloma and AKI, but the largest trial to date did not show a difference in the composite outcome of death, dialysis dependence, or eGFR <30 ml/min per m² at 6 months between the placebo and the plasmapheresis arm (15).

Until recently, only malignant monoclonal gammopathies were implicated as pathogenic and therefore warranting treatment; however, it is now recognized that some B cell or plasma cell clonal proliferative disorders may not meet hematologic criteria for a malignant monoclonal gammopathy yet can cause AKI and progressive kidney disease (e.g., monoclonal gammopathies of renal significance). These lesions are often classified on the basis of histopathology (Figure 2) and include a wide spectrum of disorders, including amyloidosis, cryoglobulinemia, monoclonal Ig deposition disease, and proximal tubular disorders like Fanconi syndrome. Data suggest that patients with monoclonal gammopathies of renal significance are at high risk for progression to kidney failure if not treated with clone-directed therapy (e.g., bortezomib) (18). Kidney biopsy should be pursued in patients with unexplained AKI, an M spike on serum protein electrophoresis, and/or an abnormal ratio of serum free light chains, as clone-directed therapy may improve kidney and hematologic outcomes (19).

Hypercalcemia

Malignancy is the most common cause of hypercalcemia among patients admitted to the ICU. Mechanisms of

hypercalcemia include secretion of parathyroid hormone-related protein (e.g., by solid tumors, T cell leukemias, and lymphomas), local osteolysis with release of cytokines, and, less commonly, ectopic parathyroid hormone secretion and tumor production of 1,25-hydroxyvitamin D. Kidney manifestations of hypercalcemia include arterial vasoconstriction leading to AKI, distal renal tubular acidosis, and nephrogenic diabetes insipidus. Management of severe hypercalcemia involves immediate, aggressive volume expansion with isotonic saline, loop diuretics in patients who develop signs or symptoms of volume overload, and calcitonin. However, these therapies each have transient effects, and patients need more definitive therapy in the form of either bisphosphonates or denosumab. Zoledronic acid is preferred in the setting of hypercalcemia of malignancy, but pamidronate or denosumab can be considered in patients with severe kidney dysfunction (20). In patients with calcium levels over 18 mg/dl, oliguric AKI, or severe neurologic symptoms, hemodialysis may be indicated.

Other Etiologies of Cancer-Associated AKI

Direct parenchymal involvement is an uncommon cause of AKI. Tumor cell infiltration of the interstitium may result in compression of the tubules and damage to the kidney vasculature, thereby leading to AKI. Leukemic or lymphomatous infiltration of the interstitium manifests as unilateral or bilateral enlargement of the kidneys; however, this is rarely the primary driver of severe AKI in patients with hematologic malignancies and is often an incidental finding (21,22). Autopsy series suggest that the prevalence

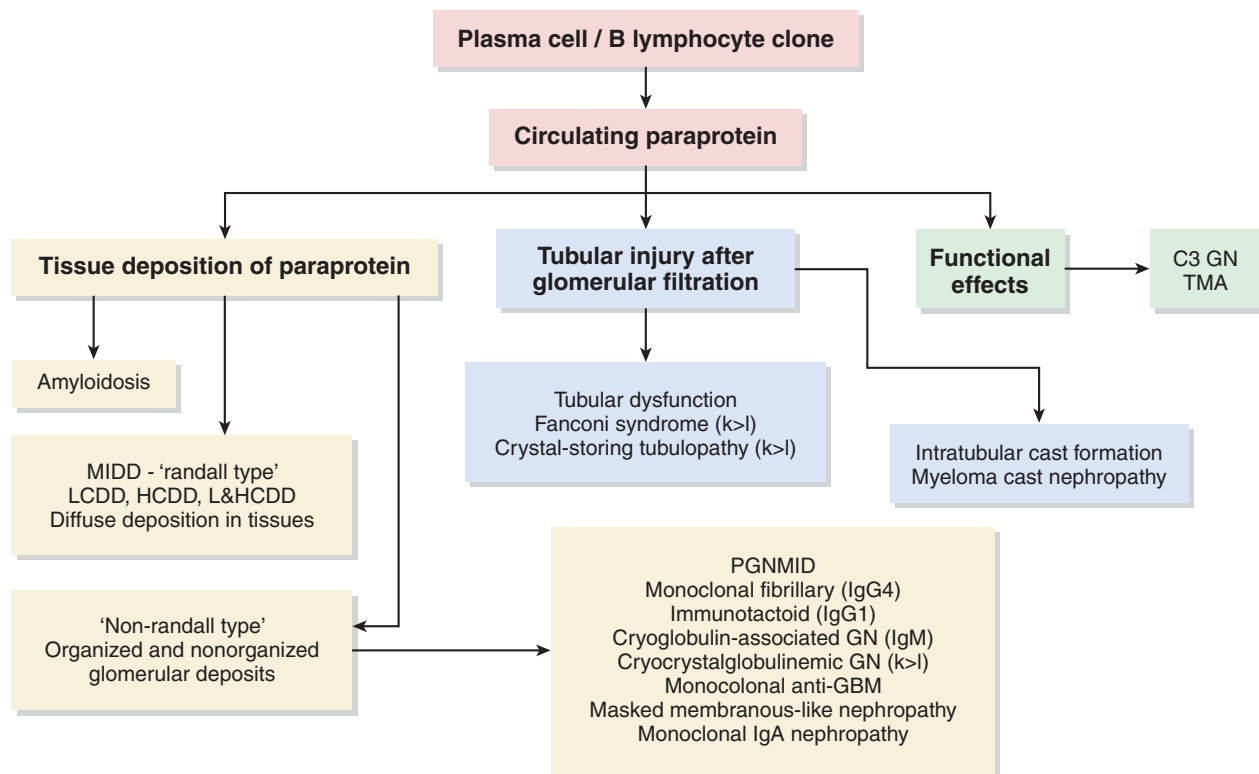


Figure 2. | Causes of AKI in monoclonal gammopathies are classified based on histopathology. C3 GN, complement 3–related GN; GBM, glomerular basement membrane; HCDD, heavy chain deposition disease; $k>l$, κ -light chain $>$ λ -light chain; LCDD, light chain deposition disease; L&HCDD, light and heavy chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease; PGNMID: proliferative GN with monoclonal Ig deposits. Adapted from Bijol and Rennke (Kidney Week 2021 presentation), with permission.

of kidney infiltration in hematologic malignancies ranges from 33% in the setting of acute myeloid leukemia to 63% in chronic lymphoblastic leukemia (23). Patients with acute myeloid leukemia and certain lymphocytic leukemias may also develop leukostasis, which can rarely cause AKI due to the formation of intravascular leukocyte thrombi and fibrin strands in the kidney vasculature (24,25). Aggressive forms of B cell lymphomas can lead to intraglomerular infiltration by tumor cells, which can manifest as nephrotic-range proteinuria, hematuria, kidney enlargement, and even severe AKI. Obstruction (both intrinsic obstruction and extrinsic compression) is a common cause of AKI, particularly in patients with genitourinary cancers. The pathophysiology and management of obstruction in patients with cancer is outlined in Figure 3.

Cancer Treatments and AKI

Conventional Chemotherapy

Conventional chemotherapies continue to be the cornerstone of treatment for many malignancies; however, several agents are associated with AKI, affecting nearly every segment of the nephron and manifesting as tubular injury, tubulointerstitial nephritis, glomerular disease, and thrombotic microangiopathy (TMA) (Table 1).

Of the platinum-based therapies, cisplatin results in the highest incidence of AKI, occurring in 32% of adults receiving a single dose (26). Cisplatin-associated AKI is dose

dependent and frequently presents as nonoliguric AKI (27). Risk factors for cisplatin-associated AKI include female sex, older age, smoking, and hypoalbuminemia (28). Proposed mechanisms include proximal tubular injury from oxidative stress and inflammation (28–30), apoptosis (31,32), mitochondrial injury (33), and DNA damage (34) (Figure 4). Therapies like intravenous fluids, mannitol, and magnesium have been proposed for the prevention of cisplatin-associated AKI; however, data from well-designed randomized controlled trials are lacking (35). Cisplatin is also associated with magnesium wasting, which may potentiate and exacerbate AKI (36). Amiloride (37) and sodium-glucose cotransporter-2 inhibitors (38) warrant further study as potential therapies for refractory hypomagnesemia.

Methotrexate is a folate derivative and antimetabolite that can cause nephrotoxicity through the accumulation of intratubular crystals, which precipitate at an acidic pH (39). Patients with a history of nephrotoxicity in the setting of high-dose methotrexate and those with preexisting CKD are at highest risk for developing methotrexate-associated AKI (40). The mainstay for prevention of MTX-associated AKI is aggressive hydration and urinary alkalization, along with discontinuation of drugs that can impair methotrexate excretion (e.g., nonsteroidal anti-inflammatory drugs and penicillin derivatives). Leucovorin is an active metabolite of folic acid and allows purine/pyrimidine synthesis to occur in the presence of methotrexate, rescuing cells from toxicity, including methotrexate-associated AKI.

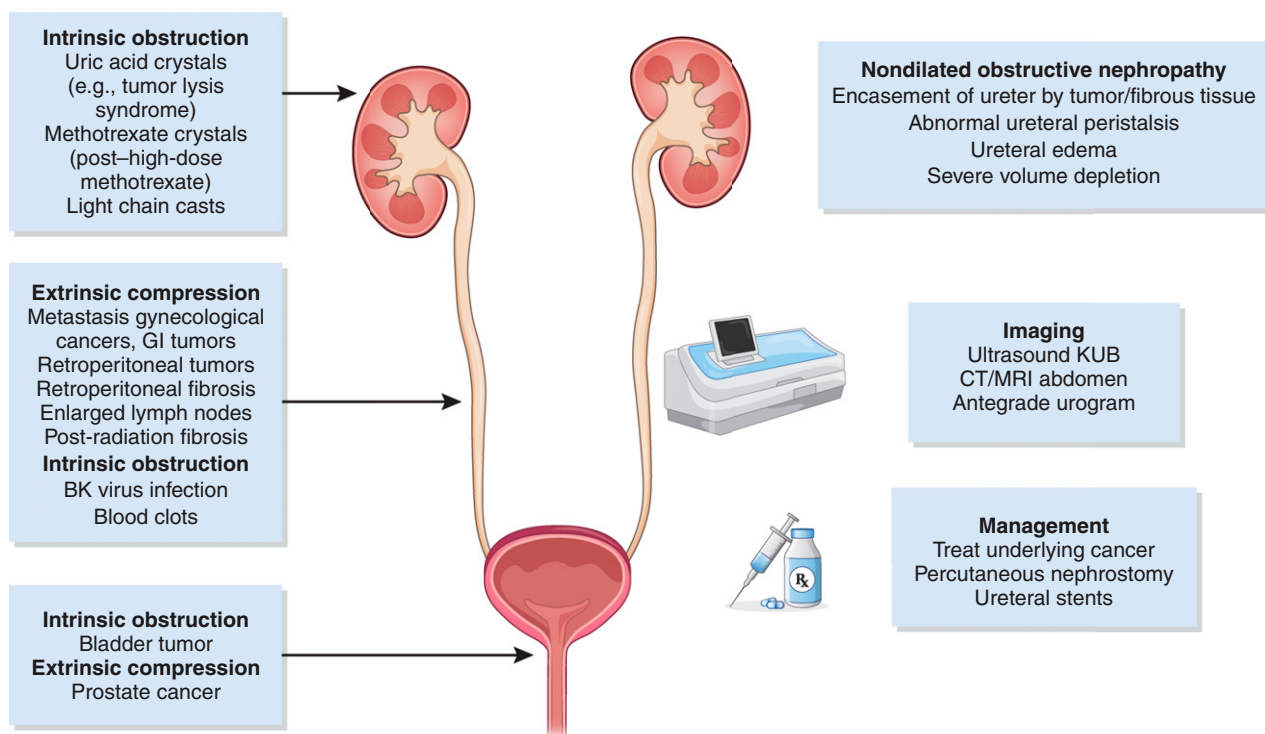


Figure 3. | Obstructive nephropathy may be extrinsic or intrinsic to the genitourinary system. CT, computed tomography; GI, gastrointestinal; KUB, kidney, ureter, bladder; MRI, magnetic resonance imaging.

Glucarpidase, a recombinant bacterial enzyme that cleaves methotrexate to inactive metabolites, is highly effective at rapidly reducing methotrexate concentrations; however, its use is limited by lack of availability and cost (41). Use of fixed dose glucarpidase should be considered for patients with 48-hour methotrexate levels >5 mmol/L and serum creatinine increases $>50\%$ from baseline (42). Dialysis has limited utility in methotrexate-associated AKI due to a rebound in plasma levels after dialysis is discontinued, although successive sessions of high-flux hemodialysis may help reduce methotrexate concentrations (43,44).

Gemcitabine is an antimetabolite used for solid organ tumors, including carcinomas of the pancreas, lung, and breast. Although relatively rare, TMA is the primary kidney lesion associated with gemcitabine. Patients typically

present with hypertension along with anemia, thrombocytopenia, increased lactate dehydrogenase levels, and low haptoglobin levels (45,46). Treatment is largely supportive; however, eculizumab has recently demonstrated some success in achieving hematologic remission in a small series of patients with severe AKI and TMA from gemcitabine (47,48). Determining which patients with chemotherapy-associated TMA should receive eculizumab remains a challenge, particularly considering its exorbitant cost. Those with diagnosed mutations in the complement inhibitory pathway (e.g., mutations in complement factor H) may stand to benefit the most, but this warrants further study.

Pemetrexed is an antifolate agent that blocks key enzymes involved in purine and pyrimidine syntheses, thereby reducing tumor cell growth and inducing apoptosis

Table 1. Nephrotoxicity associated with conventional chemotherapy

Chemotherapeutic Agent	Nephrotoxic Effect
Platins (cisplatin, carboplatin, oxaliplatin)	ATI, proximal tubulopathy, TMA, salt wasting, hypomagnesemia
Methotrexate	ATI, crystalline nephropathy
Gemcitabine	TMA
Pemetrexed	Proximal tubulopathy, ATI, nephrogenic diabetes insipidus
Ifosfamide	Proximal tubulopathy, ATI, hemorrhagic cystitis
Cyclophosphamide	Hemorrhagic cystitis, hyponatremia
Nitrosureas (carmustine, lomustine, streptozocin)	Chronic interstitial nephritis, uric acid nephrolithiasis and diabetes insipidus (streptozocin)
Mitomycin C	TMA
Melphalan	SIADH
Trabectedin	Rhabdomyolysis

ATI, acute tubular injury; TMA, thrombotic microangiopathy; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

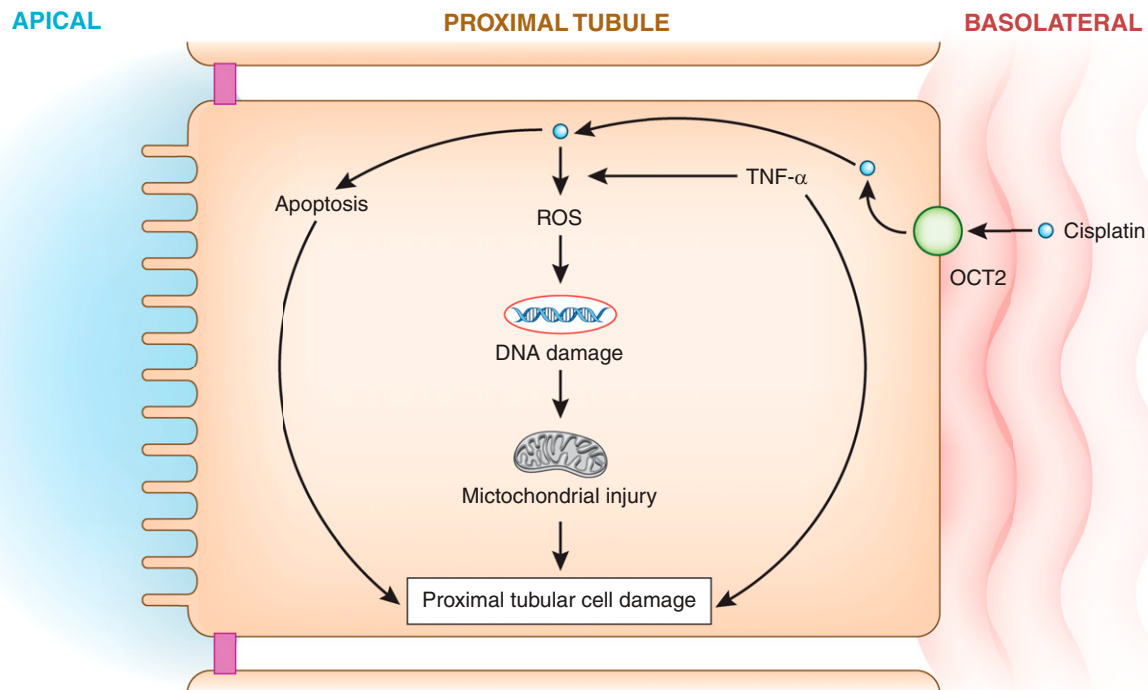


Figure 4. | Cisplatin-AKI is mediated by apoptosis, inflammation, DNA damage, and mitochondrial injury. Reactive oxygen species (ROS) are markers of oxidative stress and lead to DNA damage and mitochondrial injury. TNF- α is a proinflammatory cytokine. OCT, organic cation transporter.

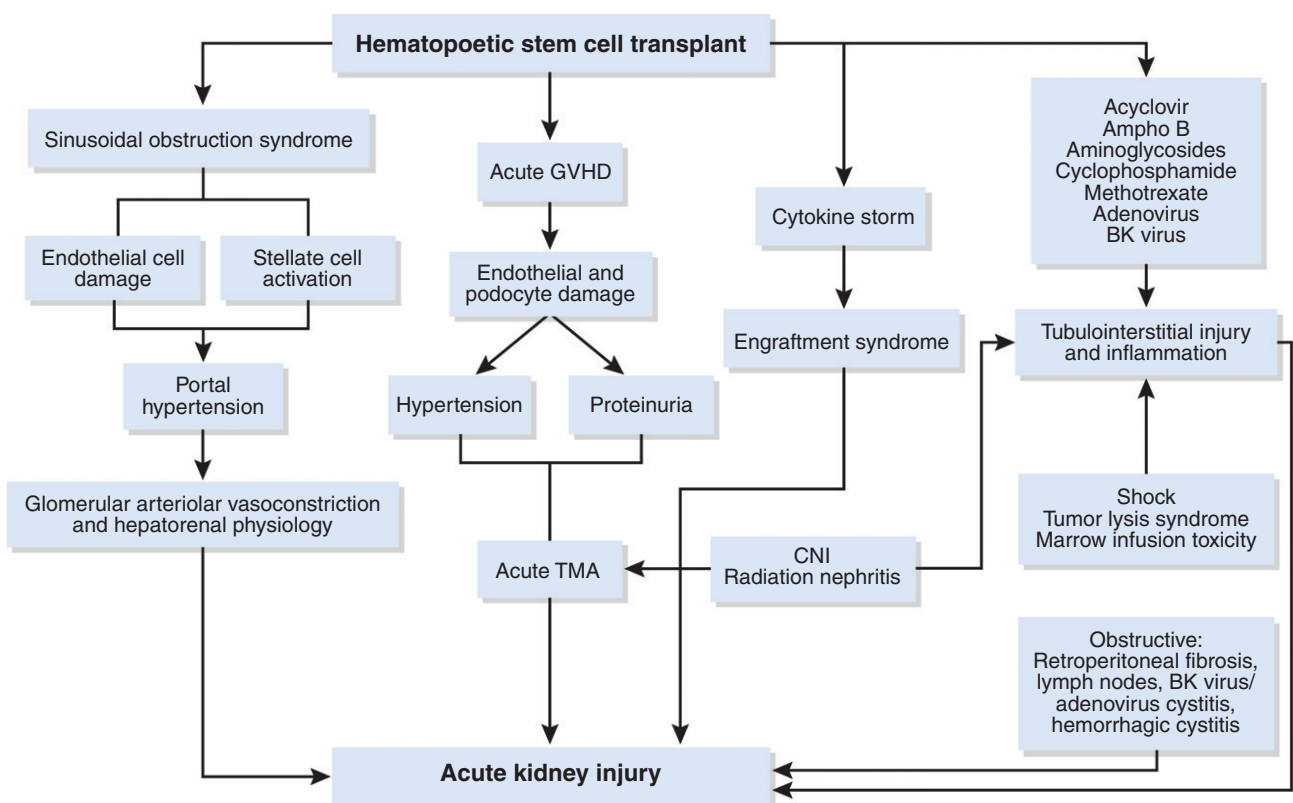


Figure 5. | The pathophysiology of AKI from HSCT is variable. AmphoB, amphotericin B; CNI, calcineurin inhibitor; GVHD, graft-versus-host disease. Adapted from ref. 122, with permission.

(49). Pemetrexed is used alone or in combination with other potentially nephrotoxic agents, such as carboplatin or cisplatin. The incidence of AKI from pemetrexed is widely variable but may be higher in patients treated with combination therapy that also includes pemetrexed, as well as in patients receiving higher cumulative doses over time (50–52). Kidney biopsies among patients presenting with AKI from pemetrexed typically show tubulointerstitial injury and tubular atrophy (53). Prevention of AKI includes minimizing concomitant nephrotoxic medications use, administration of folic acid and vitamin B12, and adequate hydration. In some cases, the drug may need to be discontinued altogether. Although pemetrexed-induced AKI may be reversible upon discontinuation, some patients may develop progressive CKD (53).

Both cyclophosphamide and ifosfamide are associated with hemorrhagic cystitis. However, ifosfamide is considered more nephrotoxic than cyclophosphamide. Biopsies of patients with AKI from ifosfamide demonstrate acute tubular necrosis and mitochondrial toxicity on electron microscopy (54). Clinically, patients with ifosfamide nephrotoxicity may present with proximal tubular dysfunction (e.g., tubular proteinuria; decreased sodium, glucose, and phosphate reabsorption; and frank glycosuria and phosphaturia). Most studies of AKI following treatment with ifosfamide have included pediatric patients (55,56), although studies in adults suggest that up to 18% develop moderate kidney dysfunction (57). Risk factors include pre-existing CKD, higher cumulative dose, and concomitant use of other potentially nephrotoxic medications (54,56,58). Guidelines for dose reduction vary considerably. There are no specific preventative therapies for ifosfamide-induced AKI. Prevention of hemorrhagic cystitis from both cyclophosphamide and ifosfamide includes aggressive hydration and use of mesna, a chemoprotective agent.

Immunotherapy

Immune checkpoint inhibitors (ICPis) have revolutionized the treatment of a wide range of malignancies. ICPis block cytotoxic T lymphocyte-associated protein 4 or programmed cell death protein 1/programmed death ligand 1, thereby increasing cytotoxic T cell activity and proliferation. Although the increased T cell activation facilitates the antitumor response of ICPis, it also can lead to immune-related adverse events, including AKI. The estimated incidence of AKI directly attributed to the immune checkpoint inhibitor (ICPi-AKI) is 2%–5%, although definitions of ICPi-AKI vary across studies (59–64).

The predominant lesion found on biopsy among patients with ICPi-AKI is acute tubulointerstitial nephritis (61,64–67), although other lesions have been described (68,69). PPIs may predispose to acute tubulointerstitial nephritis through loss of tolerance from activation of drug-specific T cells and, therefore, should be discontinued in any patient with suspected ICPi-AKI. A history of prior or concomitant extrarenal immune-related adverse events, such as rash, thyroiditis, or colitis, should raise suspicion for ICPi-AKI as well (67,70).

There are no clinical features that reliably distinguish ICPi-AKI from other potential etiologies. Although ICPi-AKI occurs at a median of 14–16 weeks (60,67), the latency

period between ICPi initiation and ICPi-AKI is highly variable, with some patients developing AKI within a few days and others developing AKI >1 year after initiation. Patients may present with sterile pyuria and subnephrotic-range proteinuria, but neither one is sensitive nor specific for ICPi-AKI (60,67).

In patients with suspected ICPi-AKI, there is considerable debate about whether patients should undergo biopsy versus empirical treatment with glucocorticoids. Guidelines published by the National Comprehensive Cancer Network recommend biopsy in patients with more than three-fold rise in serum creatinine (71). Recently, the Society for Immunotherapy Cancer acknowledged that, given the lack of specific clinical features for ICPi-AKI, kidney biopsy should be strongly considered when feasible, particularly when a plausible alternative etiology for AKI exists or urine studies are suggestive of glomerular disease (72). Patients with ICPi-AKI generally have favorable outcomes, with approximately two thirds of patients with ICPi-AKI achieving kidney recovery (67). Data suggest that early treatment with glucocorticoids is associated with a higher odds of kidney recovery (67). Data on dose and duration of glucocorticoid therapy are limited, although a single-center study showed that patients who are tapered rapidly over a median of 20 versus 38 days had equivalent outcomes (73). Although infliximab and mycophenolate mofetil have been trialed in cases of ICPi-AKI refractory to corticosteroids (67,73), larger studies are needed to determine their utility in ICPi-AKI.

One population that warrants special consideration is patients with a history of kidney transplant, due to the high risk of rejection and concerns surrounding efficacy of ICPis in patients on maintenance immunosuppression. In a multicenter study of 69 patients treated with ICPis, 29 (42%) developed acute rejection, 19 of whom lost their allograft (74). Median time to rejection was earlier (e.g., 24 days: interquartile range, 20–56). Both increasing immunosuppression and use of mammalian target of rapamycin inhibitors were associated with a lower risk of rejection. Several trials are underway that will specifically examine the role of different immunosuppressants in patients with kidney transplant receiving ICPis (NCT03816332 and NCT04339062).

Cellular Therapies

Chimeric antigen receptor T (CAR-T) cell therapy has emerged as a breakthrough therapy for hematologic malignancies, like acute lymphoblastic leukemia, recurrent B cell lymphoma, and mantle cell lymphoma, with newer generation chimeric antigen receptors now being developed for solid tumors and multiple myeloma. CAR-T cells are manufactured by genetically engineering a patient's T cells to target specific tumor antigens. These cells are expanded *ex vivo* into hundreds of millions of cells and reinfused in the patient, leading to the production of inflammatory cytokines. Cytokine release syndrome (CRS) is common after CAR-T infusion, manifesting as fever, tachycardia, and multiorgan dysfunction. AKI occurs due to cytokine-mediated capillary leak and intravascular volume depletion, with decreased kidney perfusion. Risk factors for AKI include a history of prior autologous or allogeneic stem cell transplantation, requirement for ICU-level care, and higher

grades of CRS (75). Real-world studies suggest that AKI occurs in 19%–30% of patients, usually in the context of CRS (76,77); however, the incidence is lower (5%) in patients receiving a certain type of chimeric antigen receptor, tisagenlecleucel, perhaps due to its attenuated inflammatory profile (78). Most cases of AKI present as prerenal azotemia reversible with hemodynamic support, although some patients can progress to acute tubular necrosis and the need for KRT (77). Tocilizumab, an IL-6 inhibitor, and dexamethasone may reduce the risk of CRS and therefore AKI related to CAR-T therapy (76,79).

Targeted Therapies

The introduction of novel molecularly targeted therapies in the last two decades has significantly improved patient survival compared with standard conventional chemotherapies for certain type of cancers (80). However, the toxicity profiles associated with these agents are qualitatively different from those seen with traditional cytotoxic chemotherapy and comprise a wide spectrum of pathologies (Table 2). As these targeted agents become more common in oncologic practice, it is vital that their various toxicities are recognized and investigated.

AKI after Hematopoietic Stem Cell Transplant

HSCT is a curative treatment for many benign and malignant hematologic conditions; however, patients undergoing HSCT are at high risk for AKI due to both patient-specific factors (pretransplant diabetes mellitus, hypertension, CKD, sepsis, mechanical ventilation, and ICU admission) and characteristics of HSCT (myeloablative versus nonmyeloablative) itself. The incidence of AKI ranges from 12% to 50% in myeloablative autologous HSCT, from 19% to 66% in myeloablative allogeneic HSCT, and from 29% to 54% in nonmyeloablative allogeneic SCT (81–83). The risk of needing KRT is highest in myeloablative allogeneic SCT (approximately 17%) (84). AKI occurring within 30 days of engraftment is associated with high mortality; among patients post-HSCT who are treated with KRT, the incidence of death may approach 55%–100% (85,86). Figure 5 outlines the pathophysiology of AKI in the setting of HSCT. Therapy should be directed at the underlying etiology (*e.g.*, treatment of sepsis with antibiotics, dose reduction of calcineurin inhibitors and consideration for ecilizumab in the setting of TMA [87], and use of defibrotide in hepatic sinusoidal obstruction syndrome [88]).

AKI Related to Both Cancer and Cancer-Directed Therapies

Hemodynamic-Associated AKI

Patients with cancer are susceptible to a plethora of hemodynamic insults. Nausea, vomiting, diarrhea, and anorexia occur in up to 70% of these patients, often in the setting of conventional chemotherapy with and without radiation, thereby predisposing to volume depletion and prerenal azotemia (89). Newer therapies, like ICPis, can also predispose to immune-mediated colitis and significant gastrointestinal losses, thereby leading to volume depletion (90). Even in the absence of gastrointestinal losses, hemodynamic-mediated insults can occur. Hypercalcemia,

which complicates up to 30% of all malignancies (91), can cause vasoconstriction of the afferent renal artery and degradation of aquaporins in the distal convoluted tubule, thereby predisposing to prerenal azotemia (elaborated on further in the section on Hypercalcemia) (91). Contrast-associated AKI can similarly cause kidney vasoconstriction and intraglomerular hemodynamic changes, although this is not well studied in patients with cancer (5). Other forms of hemodynamic-mediated AKI include cardiorenal syndrome from anthracyclines and the human epidermal growth factor receptor 2 modulator, trastuzumab (92), as well as hepatorenal syndrome (*e.g.*, sinusoidal obstruction syndrome post-HSCT) (93). Capillary leak is very common in patients in the ICU both with and without cancer, and it can occur due to cytokine release and increased endothelial permeability from sepsis (94) or in the postoperative setting (95). A careful medical history, physical examination, and inspection of the urine sediment can help differentiate hemodynamic causes from other etiologies of AKI and also assist with appropriate fluid management.

Thrombotic Microangiopathy

TMA is a disorder characterized by microvascular thrombosis, thrombocytopenia, microangiopathic hemolytic anemia, and end organ damage (96). TMA in patients with cancer can occur both due to the underlying malignancy as well as from the therapies used to treat it. TMA has been reported in patients with mucin-producing adenocarcinomas, in particular gastric and breast adenocarcinoma (97). The pathogenesis of cancer-associated TMA is not well understood; however, there is no evidence to support the role of ADAMTS-13 deficiency (98). One plausible mechanism for microangiopathic hemolytic anemia is red blood cell fragmentation due to direct contact with tumor emboli, as autopsies of patients with TMA demonstrate intraluminal fibrin thrombi in the blood vessels (99,100). TMA can also occur in the setting of therapies used to treat cancer. Agents commonly implicated include conventional chemotherapies (*e.g.*, gemcitabine, mitomycin C, and cisplatin) as well as targeted therapies (including antivascular endothelial growth factor inhibitors like bevacizumab, tyrosine kinase inhibitors, and selective proteasome inhibitors [*e.g.*, carfilzomib] used in the treatment of myeloma) (101). TMA in the setting of conventional chemotherapy is often dose dependent, irreversible, and associated with a high risk of progressive CKD and mortality (102). In contrast, TMA in the setting of antivascular endothelial growth factor agents is usually not dose related, is often reversible, and less reliably presents with characteristic hematologic findings. Furthermore, prognosis appears to improve with discontinuation of therapy (102). TMA can also occur after HSCT in anywhere from 2% to 39% of patients and is associated with high morbidity and mortality (103). This wide variation seen is due to a lack of fixed diagnostic criteria as well as inclusion of both adult and pediatric patients in the studies.

In general, management of TMA in patients with cancer is largely supportive and has not been shown to respond to plasma exchange or infusion (104). There are case reports and series describing successful treatment of chemotherapy-associated TMA and HSCT-TMA with ecilizumab;

Table 2. AKI from targeted therapies

Drug Class	Example	Indications	Mechanism of Toxicity	Adverse Event
VEGF inhibitors (122,123) VEGF antibody	Bevacizumab Ranibizumab Aflibercept	CRC, relapsing GBM AMD, DR AMD, DR, macular edema	Microvascular rarefaction, decrease NO, endothelial injury, podocyte injury	Hypertension, proteinuria, TMA, MCD/FGS, ATIN
Recombinant fusion protein mAb against VEGFR2 Multitargeted TKI	Ramucirumab Sunitinib Sorafenib Axitinib Pazopanib Vandetanib Cediranib Lenvatinib Motesanib Regorafenib Imatinib, dasatinib ponatinib	Gastric Ca, NSCLC, CRC RCC, GIST, pancreatic NET RCC, HCC, thyroid Ca Pancreatic Ca, RCC, CML RCC, soft tissue sarcoma Medullary thyroid Ca Relapsed ovarian Ca Advanced RCC, HCC NSCLC CRC, GIST CML		
BCR-ABL TKI (124)			Endothelial, tubular, podocyte injury	ATI (imatinib), TLS, TMA, nephrotic syndrome
Human EGFRi (125) FGFRi (126)	Trastuzumab, pertuzumab Derazatinib, dovitinib, lucantanib	Breast cancer Breast, gastric, biliary, urothelial, and SCLC	Cardiotoxicity Endothelial cell injury, decreased NO, capillary rarefaction	CRS, HTN TMA, proteinuria
BRAF inhibitors (127) Bcl-2 inhibitors (128) CDK4/6 inhibitors (121)	Vemurafenib, dabrafenib Venetoclax Palbociclib, abemaciclib, ribociclib	Metastatic melanoma CLL, SLL, AML HR+, HER2- breast Ca	Mediated by ERK activation Tubular injury Inhibit metformin uptake by OCT2; MATE1 and MATE2 transporters Endothelial cell injury	ATI, ATIN TLS, AKI Pseudo-AKI, ATI
Immunomodulators (129) mTOR inhibitors (130)	Lenalidomide, pomalidomide, thalidomide Tensirolimus, everolimus	Multiple myeloma	VEGF inhibition, reduced cubilin and megalin	AKI, ATIN, Fanconi syndrome, MCD, crystal nephropathy ATI, podocytopathies
ALK inhibitors (131)	Crizotinib, ceritinib alectinib, brigatinib lorlatinib	Small cell lung cancer	Interact with proximal tubule transporter channels, renal artery myocyte vacuolization	Pseudo-AKI, prerenal AKI, ATI, kidney cysts
PARP inhibitors (132)	Olaparib, niraparib talazoparib	BRCA-mutated breast cancer, relapsed epithelial ovarian Ca	Interact with PCT transporter channels	Pseudo-AKI
Proteasome inhibitors (133)	Bortezomib, ixazomib, carfilzomib	Multiple myeloma, MCL	Direct microvascular toxicity; cytokines leading to autoantibody formation	TMA, HTN
Bruton tyrosine kinase inhibitor (134) XPO 1 inhibitor (135) CD22-directed cytotoxin (136)	Ibrutinib Selinexor Moxetumomab pasudotox	CLL/SLL, MCL, WM, marginal zone lymphoma Multiple myeloma Hairy cell leukemia	Endothelial and tubular injury Nausea and vomiting Capillary leak syndrome, nausea/vomiting	Hypertension, TLS ATI Prerenal AKI, hyponatremia Prerenal AKI, HUS
VEGF, vascular endothelial growth factor; NO, nitric oxide; TMA, thrombotic microangiopathy; MCD, minimal change disease; ATIN: acute tubulointerstitial nephritis; CRC, colorectal cancer; GBM, glioblastoma multiforme; AMD, age-related macular degeneration; DR, diabetic retinopathy; VEGFR2, vascular endothelial growth factor receptor 2; Ca, carcinoma; NSCLC, nonsmall cell lung cancer; TKI, tyrosine kinase inhibitor; RCC, renal cell cancer; GIST, gastrointestinal stromal tumor; NET, neuroendocrine tumor; HCC, hepatocellular carcinoma; CML, chronic myeloid leukemia; BCR-ABL, breakpoint cluster region-tyrosine protein kinase ABL-1 gene; ATI, acute tubular injury; TLS, tumor lysis syndrome; EGFRi, epidermal growth factor receptor inhibitor; CRS, cytokine release syndrome; HTN, hypertension; FGFRi, fibroblast growth factor receptor inhibitor; SCLC, small cell lung cancer; BRAF, proto-oncogene B-raf; ERK, extracellular signal-regulated kinase; Bcl-2, B cell lymphoma-2 gene; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; AML, acute myeloid leukemia; CDK4/6, cyclin-dependent kinase 4/6; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; OCT2, organic cation transporter 2; MATE, multidrug and toxin extrusion; mTOR, mammalian target of rapamycin; ALK, anaplastic lymphoma kinase; PARP, poly-ADP-ribose polymerase; BRCA, breast cancer gene; PCT, proximal convoluted tubule; MCL, mantle cell lymphoma; WM, Waldenstrom macroglobulinemia; XPO 1, exportin-1; CD22, cluster differentiation-22; HUS, hemolytic uremic syndrome.				

however, larger studies are needed to verify these findings (48,87,105,106).

Tumor Lysis Syndrome

Tumor lysis syndrome is a constellation of metabolic derangements, namely hyperkalemia, hyperphosphatemia, and hyperuricemia, that results from the rapid degradation of tumor cells. Tumor lysis syndrome is considered an oncologic emergency due to the risk of life-threatening arrhythmias and respiratory failure as well as AKI. It can occur spontaneously but most often develops during treatment of hematologic malignancies. Tumor lysis syndrome can also occur following use of targeted therapies, like venetoclax, bortezomib, and rituximab, as well as BRAF/MEK inhibitors (107–111). Tumor cell breakdown results in the release of purines, which are converted to intermediate products (e.g., hypoxanthine and xanthine) and then metabolized to uric acid (Figure 6). AKI occurs secondary to calcium phosphate and uric acid deposition, although uric acid can also perpetuate AKI through crystalline-independent pathways, including inflammation and kidney vasoconstriction, as well as decreased kidney perfusion (112–114). Tumor lysis syndrome is classified using the Cairo-Bishop criteria, which define laboratory tumor lysis syndrome as a 25% decrease in serum calcium and/or a 25% increase in uric acid, potassium, or phosphate levels from baseline (115). These abnormalities must occur within 3 days preceding or 7 days following the initiation of chemotherapy. Clinical tumor lysis syndrome is defined as laboratory tumor lysis syndrome in addition to clinical manifestations, such as arrhythmia, seizures, AKI, or sudden death.

Prevention involves aggressive volume repletion for all patients at risk for tumor lysis syndrome to maintain high urinary flow rates and promote uric acid, potassium, and

phosphate excretion. Urinary alkalization is no longer recommended due to the risk of calcium-phosphate precipitation. Allopurinol and febuxostat are xanthine oxidase inhibitors that are recommended for prophylaxis in patients with low to intermediate risk of tumor lysis syndrome. Importantly, allopurinol has no effect on preexisting uric acid levels. Furthermore, the manufacturer's label suggests that the dose of allopurinol should be reduced in patients with a creatinine clearance below 20 ml/min (116), and therefore, caution should be used with higher doses in the setting of severe oliguric AKI. High-risk patients may benefit from rasburicase, a recombinant urate oxidase that converts uric acid to its more soluble form, allantoin. Rasburicase has been shown to rapidly reduce uric acid levels in both pediatric and adult patients at high risk for tumor lysis syndrome (117,118), but it is contraindicated in the setting of glucose-6-phosphate dehydrogenase deficiency due to the risk of severe hemolysis. Some patients may require early initiation of KRT to increase clearance of potassium, phosphate, and uric acid.

Future Directions

In the era of precision medicine, there is considerable interest in identifying biomarkers of AKI, and this extends to the field of onconeurology as well. Markers of AKI, like serum creatinine, rise only after significant injury has occurred and have decreased utility in patients with reduced muscle mass. Although several novel markers for early diagnosis of AKI show promise in preclinical studies, few have been sufficiently evaluated in patients with cancer, and most are markers of tubular injury studied in the context of cisplatin nephrotoxicity. More recent studies have explored whether certain blood and urine biomarkers are associated with nephrotoxicity from immunotherapy. For example, one single-center, retrospective study identified higher levels of C-reactive protein and urinary retinol binding protein in patients with ICPI-AKI and, specifically, in those with acute tubulointerstitial nephritis as the dominant lesion on kidney biopsy (119).

Biomarkers may also help differentiate “pseudo-AKI” from true AKI. For instance, both poly-ADP-ribose polymerase inhibitors and cyclin-dependent kinase 4/6 have been associated with pseudo-AKI (120,121) (Table 2), with elevations in serum creatinine without a true decline in GFR. Measurement of cystatin C levels and kidney iohalate clearance may help differentiate pseudo-AKI from true AKI, but additional biomarkers with anatomic specificity are urgently needed. The paucity of data on biomarkers in onconeurology is due in part to the lack of a “gold standard,” where patients are often treated empirically for their AKI, irrespective of the cause. Furthermore, our understanding of the mechanisms underlying AKI in patients with cancer is limited, highlighting the need for larger translational studies with longitudinal biospecimen collection.

AKI has major repercussions for patients with cancer and can lead to ineligibility for further therapy, prolonged hospitalizations, and higher mortality. As patients with cancer are living longer, they must also grapple with the sequelae of recurrent AKI events, including CKD. A more thorough

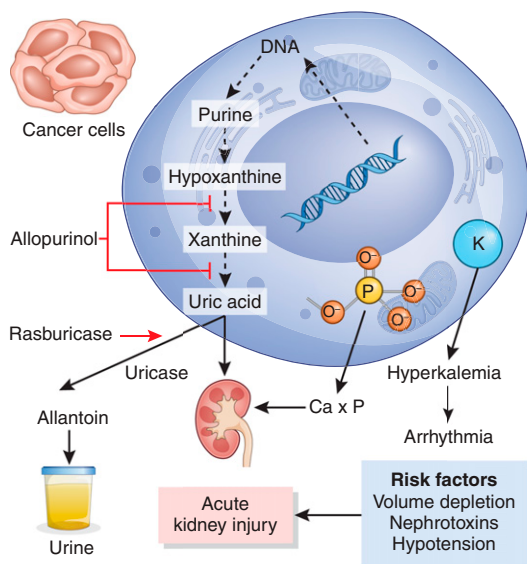


Figure 6. | Pathophysiology of AKI in the setting of TLS and therapeutic targets. Allopurinol inhibits xanthine oxidase, an enzyme that converts hypoxanthine to xanthine and xanthine to uric acid. Rasburicase is a recombinant urate oxidase that converts uric acid into a more soluble metabolite, allantoin. Ca×P, calcium phosphate product; K, potassium.

understanding of both patient- and cancer-specific predisposing risk factors is needed to help risk-stratify patients and optimize their cancer care. Furthermore, large-scale genetic and biomarker-based studies may provide insight into potential therapeutic targets. Given the complexities of managing AKI in the patient with cancer, a multidisciplinary team of hematologists, oncologists, and nephrologists is needed to provide quality care to this vulnerable subset of patients.

Disclosures

K.D. Jhaveri reports employment with Northwell Health; is a founder and copresident of the American Society of Onco-Nephrology; reports consultancy agreements with Astex Pharmaceuticals, ChemoCentryx, Chinook, GlaxoSmithKline, Natera, and Trave Therapeutics; reports honoraria from the American Society of Nephrology, the International Society of Nephrology, and UpToDate.com; reports serving on the editorial boards of *American Journal of Kidney Diseases*, *CJASN*, *Clinical Kidney Journal*, *Journal of Onconephrology*, *Kidney International*, and *Nephrology Dialysis Transplantation*; reports serving as Editor-in-Chief of *ASN Kidney News* and section editor for onconephrology for *Nephrology Dialysis Transplantation*; and reports other interests/relationships as the President of American Nephrologist of Indian Origin. P. Gudsoorkar reports serving as an editorial board member for *Advances in Chronic Kidney Disease*; serving as a scientific advisor or member of the medical advisory board of the National Kidney Foundation–Northern Kentucky & Southern Ohio; and serving as a member and fellow of the National Kidney Foundation. S. Gupta reports research funding from BTG International and GE HealthCare and is a founder and copresident of the American Society of Onco-Nephrology.

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Author Contributions

S. Gupta, P. Gudsoorkar, and K.D. Jhaveri were responsible for visualization; P. Gudsoorkar and S. Gupta wrote the original draft; and P. Gudsoorkar, S. Gupta, and K.D. Jhaveri reviewed and edited the manuscript.

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S.G. and P.G. contributed equally to this work.

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