

## REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

## Acute Kidney Injury in Patients with Cancer

Mitchell H. Rosner, M.D., and Mark A. Perazella, M.D.

From the Division of Nephrology, University of Virginia Health System, Charlottesville (M.H.R.); and the Section of Nephrology, Yale University School of Medicine, New Haven, and the Veterans Affairs Medical Center, West Haven — both in Connecticut (M.A.P.). Address reprint requests to Dr. Rosner at the Division of Nephrology, University of Virginia Health System, Box 800133, Charlottesville, VA 22908, or at mhr9r@virginia.edu.

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ACUTE KIDNEY INJURY IS COMMON IN PATIENTS WITH CANCER<sup>1,2</sup>; THE incidence and severity vary, depending on the type and stage of cancer, the treatment regimen, and coexisting conditions.<sup>3</sup> In a 7-year Danish study of 37,267 incident cases of cancer, the 1-year risk of acute kidney injury, as defined by the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) classification (Table 1), was 17.5%.<sup>4</sup> The 5-year risk for the individual risk, injury, and failure categories was 27.0%, 14.6%, and 7.6%, respectively. Furthermore, 5.1% of patients in whom acute kidney injury developed required long-term dialysis within 1 year.<sup>4</sup>

Patients with cancer who are critically ill have the highest risk of acute kidney injury (incidence, 54%),<sup>5</sup> particularly patients who have hematologic cancers or multiple myeloma and those with septic shock.<sup>6</sup> This review provides an overview of acute kidney injury in patients with cancer.

## RISK FACTORS FOR ACUTE KIDNEY INJURY

Patients with cancer are at risk for acute kidney injury that is caused by sepsis, direct kidney injury due to the primary cancer, metabolic disturbances, the nephrotoxic effects of anticancer therapies, or hematopoietic stem-cell transplantation.<sup>7-9</sup> Older age (>65 years), female sex, and coexisting disease processes, including chronic kidney disease, diabetic kidney disease, and volume depletion (due to vomiting or diarrhea) or renal hypoperfusion (due to cardiomyopathy, cirrhosis, or the nephrotic syndrome), increase the risk of acute kidney injury.<sup>10</sup>

## OUTCOMES IN PATIENTS WITH CANCER AND ACUTE KIDNEY INJURY

Acute kidney injury in patients with cancer is associated with substantial morbidity and mortality.<sup>3,11,12</sup> In a study involving patients with hematologic cancers who were undergoing induction therapy, the 8-week mortality was 13.6% among patients in the RIFLE risk category and was 61.7% among those in the failure category who required dialysis, as compared with 3.8% among patients without any evidence of acute kidney injury.<sup>11</sup> In another study, among patients with cancer who were in the intensive care unit, the mortality was 49.0% for those in the RIFLE risk category, 62.3% for those in the injury category, and 86.8% for those in the failure category, as compared with 13.6% for patients without acute kidney injury.<sup>5</sup> However, increased mortality has not been reported in all studies, possibly owing to differences among studies in the age, overall severity of illness, and functional status of the patients.<sup>13</sup>

Acute kidney injury increases the risk of toxic effects from systemic chemotherapy, jeopardizes the continuation of cancer therapy, and limits patient partici-

pation in possibly life-saving clinical trials. Among patients being treated with potentially curative regimens, acute kidney injury may necessitate dose reductions or use of alternative regimens that have better renal safety records but marginal efficacy.<sup>2,14</sup>

#### CANCERS ASSOCIATED WITH ACUTE KIDNEY INJURY

##### HEMATOLOGIC CANCERS OTHER THAN MYELOMA

Acute kidney injury occurs in up to 60% of patients with hematologic cancers at some point in the disease course,<sup>15,16</sup> most commonly in association with sepsis, nephrotoxins, the tumor lysis syndrome (especially with rapidly growing cancers such as Burkitt's lymphoma), or volume depletion.<sup>16-18</sup> Other, less common associations must also be considered in the differential diagnosis (Table 2).

The kidney is the most common extrarenal site of leukemic and lymphomatous infiltration, and tumor-cell infiltrates in the kidney are seen in up to 30% of patients with lymphoma and up to 60% of patients on autopsy.<sup>19,20</sup> However, renal infiltration causes acute kidney injury in only 1% of patients with acute leukemia and in even fewer patients with lymphoma or chronic leukemia.<sup>21,22</sup> In patients with massive tumor-cell infiltration, tubular compression and disruption of the microcirculation set the stage for acute kidney injury. Flank pain and hematuria, along with hypertension, may accompany acute kidney injury, although many patients are asymptomatic. Renal imaging with ultrasonography or computed tomography generally shows bilaterally enlarged kidneys. A kidney biopsy is diagnostic, revealing diffuse infiltration of the interstitium with malignant cells that can be identified with specific stains and immunologic markers. Prompt administration of chemotherapy may lead to rapid improvement in kidney function; the long-term prognosis depends on the response to therapy.<sup>21</sup>

##### MULTIPLE MYELOMA

Acute kidney injury complicates multiple myeloma in, depending on the definition used, 20 to 50% of patients.<sup>23-25</sup> Nephrotoxic effects often develop from overproduction of monoclonal immunoglobulins and free light chains, leading to cast nephropathy (the most common cause of acute

**Table 1. RIFLE (Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease) Classification of Acute Kidney Injury.\***

Classification of Injury	Change in Kidney Function
Risk	Cr increased by 1.5 times or GFR decreased by >25%
Injury	Cr increased by 2 times or GFR decreased by >50%
Failure	Cr increased by 3 times or GFR decreased by >75%, or Cr >0.5 mg/dl (44 μmol/liter) if baseline value ≥4 mg/dl (350 μmol/liter)
Loss of kidney function	Complete loss of kidney function for >4 wk
End-stage kidney disease	Complete loss of kidney function for >3 mo

\* Cr denotes serum creatinine, and GFR glomerular filtration rate.

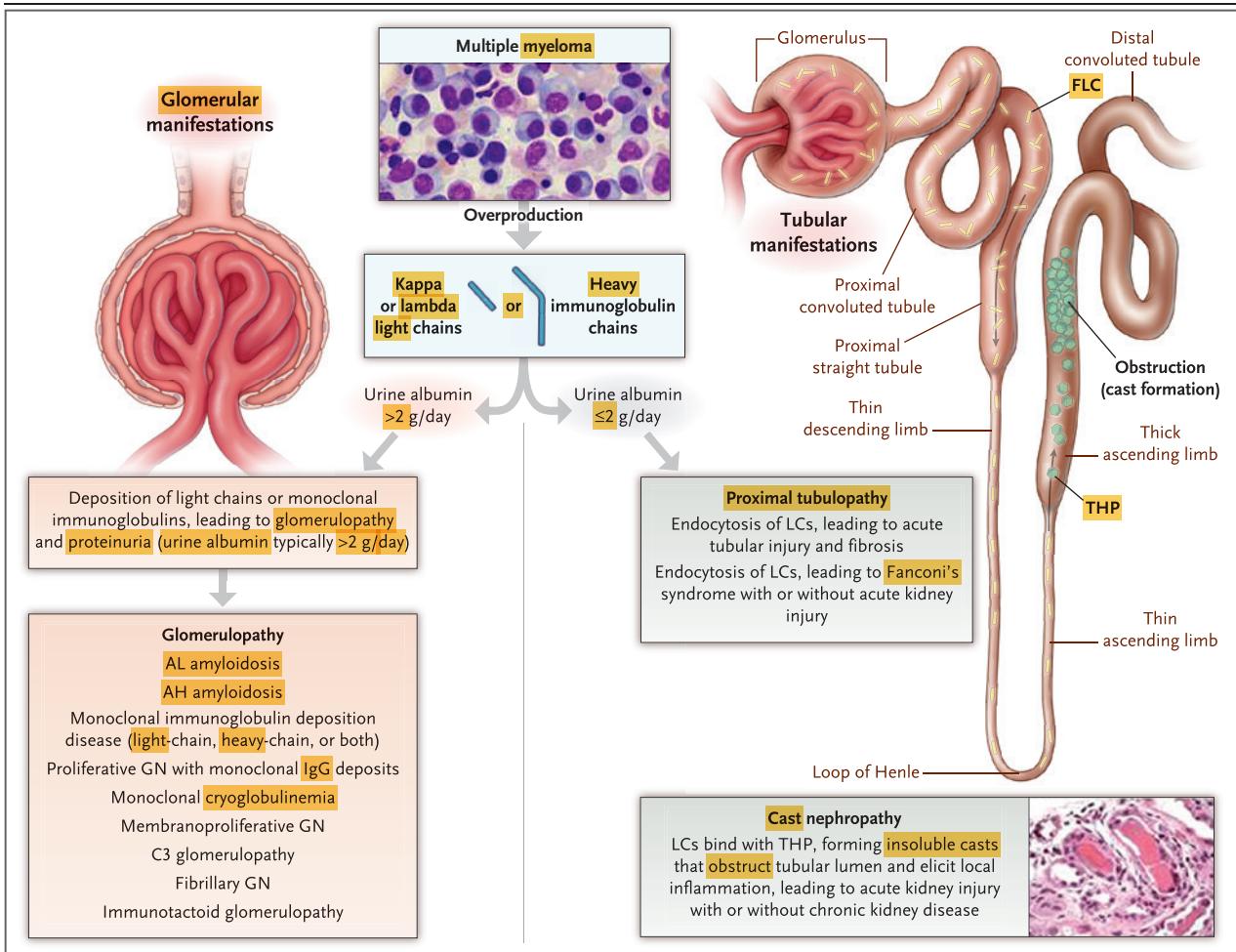
**Table 2. Types of Acute Kidney Injury in Patients with Hematologic Cancers.\***

<b>Cancer-related injury</b>
Tumor infiltration of the kidneys
Obstructive nephropathy related to retroperitoneal lymphadenopathy
Lysozymuria (CMML or AML) with direct tubular injury
Hemophagocytic lymphohistiocytosis with acute interstitial disease
Vascular occlusion associated with DIC and hyperleukocytosis (rare)
Hypercalcemia with hemodynamic acute kidney injury and acute nephrocalcinosis
Glomerular diseases (minimal change disease, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, membranous nephropathy, amyloidosis, immunotactoid glomerulonephritis, fibrillary glomerulonephritis, crescentic glomerulonephritis)†
<b>Therapy-related injury</b>
Nephrotoxicity (including thrombotic microangiopathy, acute tubular injury, tubulointerstitial nephritis, and glomerular disease)
Tumor lysis syndrome with acute uric acid nephropathy (may occur spontaneously)
Intratubular obstruction from medications (e.g., methotrexate)
<b>Other types of injuries</b>
Volume depletion
Sepsis and septic shock
Nephrotoxicity of radiocontrast agents
Nephrotoxicity of common medications, such as NSAIDs, ACE inhibitors, ARBs, and antibiotics

\* ACE denotes angiotensin-converting enzyme, AML acute monocytic leukemia, ARBs angiotensin-receptor blockers, CMML chronic myelomonocytic leukemia, DIC disseminated intravascular coagulation, and NSAIDs nonsteroidal antiinflammatory drugs.

† Reported associations with focal segmental glomerulosclerosis, membranous nephropathy, and crescentic glomerulonephritis are rare.

kidney injury), light-chain-related proximal tubular injury, and various glomerulopathies such as light-chain deposition disease and amyloid light-chain (AL) amyloidosis. Furthermore, metabolic



**Figure 1. Diagnostic Approach to Patients Presenting with Acute Kidney Injury and Suspected Myeloma.**

In patients with multiple myeloma, various glomerular and tubular manifestations can develop. Either isolated light (kappa or lambda) or heavy immunoglobulin chains can lead to injury. Patients with urine albumin levels higher than 2 g per day usually have one of a variety of glomerular lesions, whereas patients with lower urine albumin levels usually have a proximal tubulopathy or cast nephropathy. The stains are Wright–Giemsa (multiple myeloma) and hematoxylin and eosin (cast nephropathy). AH denotes amyloid heavy chain, AL amyloid light chain, FLC free light chain, GN glomerulonephritis, LC light chain, and THP Tamm–Horsfall protein.

disturbances (e.g., hypercalcemia and hyperuricemia), sepsis, and nephrotoxin exposure may lead to acute kidney injury and may exacerbate paraprotein-related kidney injury. Factors associated with acute kidney injury in patients with myeloma are shown in Figure 1.

Cast nephropathy develops when large amounts of free light chains, which are filtered at the glomerulus, bind to Tamm–Horsfall protein (uromodulin) in the tubules, forming insoluble casts that cause intrarenal obstruction and subsequent tubulointerstitial inflammation.<sup>26</sup> An-

other key mechanism of injury is proximal tubular reabsorption of massive amounts of free light chains, leading to activation of inflammatory cytokines, oxidative stress, apoptosis, and ultimately, fibrosis.<sup>27,28</sup> Thus, a decrease in the glomerular filtration rate due to increased intraluminal tubular pressure, together with local interstitial inflammation and acute tubular injury, results in acute kidney injury.<sup>24</sup>

The diagnosis of cast nephropathy is facilitated by measurement of serum free light chains with the use of a nephelometric immunoassay

(quantitative measurement of both kappa and lambda free light chains) and serum protein electrophoresis supplemented with spot or 24-hour urine protein electrophoresis.<sup>24,29</sup> These tests help to distinguish paraprotein-related glomerular diseases (often associated with massive proteinuria) from cast nephropathy (associated with free light chains).<sup>30</sup> Although high free light-chain levels in both serum and urine are consistent with acute kidney injury due to cast nephropathy, kidney biopsy should be performed if the diagnosis is uncertain, since in more than 15% of patients with acute kidney injury, the cause is unrelated to their myeloma.<sup>31</sup>

Current therapy for cast nephropathy includes adequate hydration, correction of hypercalcemia, and chemotherapy to reduce the free light-chain level rapidly. With such therapy, the survival of patients with acute kidney injury has improved; a clinically significant reduction in free light chains within 3 weeks after diagnosis is associated with a high likelihood of full or partial renal recovery.<sup>32-34</sup> Accordingly, the incidence of and mortality associated with end-stage renal disease due to multiple myeloma decreased from 2001 to 2010.<sup>35</sup>

Effective chemotherapeutic regimens for patients with myeloma who present with acute kidney injury generally include the proteasome inhibitor bortezomib, which does not require dosage adjustments for acute kidney injury.<sup>36</sup> In a European prospective, randomized, phase 3 trial involving a subgroup of 81 patients with a serum creatinine level of at least 2 mg per deciliter (177  $\mu$ mol per liter), patients who received bortezomib, doxorubicin, and dexamethasone had a significantly higher rate of overall survival at 3 years than those who received treatment with vincristine, doxorubicin, and dexamethasone (74% vs. 34%).<sup>37</sup> In a more recent study, involving 83 consecutive patients with myeloma and an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m<sup>2</sup> of body-surface area, bortezomib-based triple therapy (bortezomib, dexamethasone, and another agent such as melphalan or thalidomide) was associated with a 72% renal response rate, and dialysis was discontinued in 57% of the patients.<sup>38</sup> Other agents reported as being effective in patients with myeloma and acute kidney injury include thalidomide, lenalidomide, and two newer agents,

pomalidomide (a thalidomide analogue) and carfilzomib.<sup>34,39,40</sup> Hematopoietic stem-cell transplantation appears to be a viable option for patients with renal injury, including those on dialysis. A large series showed an excellent hematologic response but a low rate of renal improvement.<sup>41</sup>

In addition to therapy to reduce free light-chain production, free light chains are potentially amenable to removal by therapeutic plasma exchange or hemodialysis with the use of large-pore hemofilters (high-cutoff hemodialysis). Small randomized, controlled trials, which were determined later to be flawed, showed no benefit, and small studies with positive findings were not controlled. Thus, plasma exchange cannot currently be recommended.<sup>42</sup> Results from two European randomized, controlled trials of high-cutoff hemodialysis are awaited: the European Trial of Free Light Chain Removal by Extended Haemodialysis in Cast Nephropathy (EuLITE; ClinicalTrials.gov number, NCT00700531) and Studies in Patients with Multiple Myeloma and Renal Failure Due to Myeloma Cast Nephropathy (MYRE; NCT01208818).<sup>43,44</sup>

#### RENAL-CELL CARCINOMA

Treatment of renal-cell carcinoma has evolved to include less-invasive and renal-sparing techniques, in part to protect patients from acute kidney injury and the subsequent risk of chronic kidney disease. Surgical treatment of renal-cell carcinoma is associated with a substantial risk of acute kidney injury; the reported rate of post-surgical acute kidney injury increased from 2.0% in 1998 to 10.4% in 2010.<sup>45</sup> However, changes in the definition of acute kidney injury may be responsible for these figures, since the number of patients in whom dialysis-requiring acute kidney injury developed rose minimally during this period.<sup>45,46</sup> The rate of acute kidney injury is higher after radical nephrectomy than after partial nephrectomy<sup>45-47</sup>; for this reason, existing guidelines recommend partial nephrectomy whenever technically feasible or, in some cases, active surveillance of small renal masses without surgery in an effort to maintain kidney function and optimize outcomes.<sup>48</sup> Recent advances in percutaneous ablative techniques may lead to further reductions in the incidence of acute kidney injury, but more data on these techniques are required.<sup>49</sup>

**METABOLIC DISTURBANCES  
ASSOCIATED WITH ACUTE KIDNEY  
INJURY**

**TUMOR LYSIS SYNDROME**

The tumor lysis syndrome results from the release of intracellular electrolytes and nucleic acids from malignant cells that were lysed by anti-cancer therapies or, in rare circumstances, spontaneously.<sup>50</sup> Nearly all hematologic and solid-organ cancers have been associated with the tumor lysis syndrome, but it is much more common with large, chemosensitive tumor burdens that have a high proliferative rate, such as Burkitt's lymphoma and acute lymphoblastic leukemia. The tumor lysis syndrome is characterized by increases in serum levels of uric acid, potassium, and phosphorus and can be accompanied by hypocalcemia.<sup>51</sup> Cardiac arrhythmias and even sudden death may occur from metabolic derangements such as hyperkalemia. The syndrome may be associated with acute kidney injury and seizures. The actual frequency of acute kidney injury among patients with the tumor lysis syndrome is unknown and probably varies according to tumor characteristics and coexisting disorders, as well as the chemotherapeutic regimen and preventive measures used. Within the kidney, cytokine release associated with acute tubular injury, acute uric acid nephropathy, and acute nephrocalcinosis may contribute to the development of acute kidney injury.<sup>52</sup>

Uric acid nephropathy results when purine nucleotides released from cancer cells are metabolized by xanthine oxidase into insoluble uric acid. Very high levels of uric acid in the glomerular filtrate may precipitate in the renal tubules, leading to micro-obstruction and vasoconstriction, as well as renal ischemia and up-regulation of inflammatory cytokines, and resulting in an abrupt decrease in the glomerular filtration rate.<sup>53</sup> Calcium phosphate precipitation in the renal tubules may also contribute to acute kidney injury in patients with severe hyperphosphatemia from the tumor lysis syndrome, especially if the urine is alkaline.<sup>54</sup> Although urinary alkalinization increases uric acid solubility, alkalinization is not currently recommended, since it can lead to increased calcium phosphate precipitation.<sup>50,52</sup>

The tumor lysis syndrome can be prevented (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org)

by maintaining an adequate glomerular filtration rate and high urine flow rates through appropriate intravenous hydration (normal saline), which allows for rapid and effective clearance of uric acid, potassium, and phosphorus.<sup>50,52</sup> In patients at high risk for the tumor lysis syndrome, prophylactic use of xanthine oxidase inhibitors, such as allopurinol or febuxostat, which block the production of uric acid, is recommended.<sup>50,52,55</sup> Patients whose uric acid levels are high before the initiation of chemotherapy may benefit from treatment with rasburicase (recombinant urate oxidase) before chemotherapy is administered.<sup>56,57</sup> Rasburicase converts uric acid to the more soluble allantoin; it also leads to the production of hydrogen peroxide, which can cause methemoglobinemia and hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Thus, patients at risk for G6PD deficiency should be tested for it before they receive rasburicase.<sup>58</sup>

Management of the tumor lysis syndrome follows the same approaches as prophylaxis: aggressive intravenous hydration, xanthine oxidase inhibition to prevent further uric acid production, and administration of rasburicase to rapidly lower serum uric acid levels.<sup>56,57</sup> Given the increased use of rasburicase for the tumor lysis syndrome, acute kidney injury from acute nephrocalcinosis may become more common in patients with this syndrome, highlighting the importance of normalizing the serum phosphorus level and avoiding urinary alkalinization.<sup>59</sup>

**HYPERCALCEMIA OF MALIGNANCY**

Hypercalcemia occurs in up to 30% of patients with advanced cancer.<sup>60</sup> Most studies suggest that squamous-cell carcinoma of the lung is the most common cancer associated with hypercalcemia (up to 20% of patients with hypercalcemia have squamous-cell carcinoma of the lung) as a result of paraneoplastic secretion of parathyroid hormone-related protein.<sup>61</sup> Hypercalcemia also occurs in patients with adenocarcinomas and hematologic cancers.<sup>62</sup>

Hypercalcemia of malignancy often leads to acute kidney injury, which in turn may exacerbate hypercalcemia by limiting renal calcium excretion. Several mechanisms lead to hypercalcemia-related acute kidney injury: activation of the calcium-sensing receptor in the thick ascending limb of Henle, which inhibits the sodium-potassium-

chloride cotransporter and leads to marked natriuresis and volume depletion; nausea, vomiting, and ileus with resultant volume depletion; calcium-induced renal vasoconstriction with resultant decreases in renal blood flow<sup>63,64</sup>; nephrogenic diabetes insipidus; and acute nephrocalcinosis from severe hypercalcemia (and hyperphosphatemia).

Treatment of hypercalcemia-induced acute kidney injury relies on restoration of intravascular volume and renal perfusion, an increase in the glomerular filtration rate, and rapid lowering of the serum calcium level, followed by a sustained therapeutic phase focused on maintaining a normal serum calcium level. The first step in therapy is aggressive intravenous hydration with 0.9% normal saline (200 to 250 ml per hour). Loop diuretics are of little benefit, since they increase excretion of renal calcium, which may precipitate in the kidney, and also confer a risk of hypovolemia. Thus, diuretics should be used only in patients with hypervolemia.<sup>65</sup> Severe cases of acute kidney injury, which are often characterized by oligoanuria, may not be amenable to intravenous hydration, whereas hemodialysis with a low calcium dialysate effectively corrects hypercalcemia.<sup>66</sup> After this initial therapeutic stage, medications that diminish bone calcium release (bisphosphonates, calcitonin, or both) are used to maintain normocalcemia. If pamidronate is used for bisphosphonate therapy, the dose must be adjusted for kidney function; zoledronic acid should be avoided. A newer therapeutic option that does not require dosing modification is denosumab, a humanized monoclonal antibody that neutralizes the receptor activator of nuclear factor- $\kappa$ B ligand and reduces osteoblast activity and bone calcium release.<sup>67</sup> Recent studies support the use of denosumab in patients with cancer-associated hypercalcemia.<sup>68,69</sup>

#### HEMATOPOIETIC STEM-CELL TRANSPLANTATION AND ACUTE KIDNEY INJURY

Hematopoietic stem-cell transplantation is frequently complicated by acute kidney injury.<sup>70</sup> The published incidence of acute kidney injury associated with hematopoietic stem-cell transplantation is wide-ranging (10% to 73%), primarily because of variations in the definition of acute kidney injury, the type of transplant used (allo-

geneic vs. autologous), and the chemotherapeutic conditioning regimen (high-dose vs. reduced-intensity).<sup>70</sup> Approximately 5% of hematopoietic stem-cell transplant recipients with severe acute kidney injury require dialysis.<sup>71,72</sup>

Common risk factors for and causes of acute kidney injury after transplantation include volume depletion, sepsis, nephrotoxic medications, graft-versus-host-disease (GVHD), and the sinusoidal obstruction syndrome.<sup>73,74</sup> GVHD, a complication of hematopoietic stem-cell transplantation, causes tissue and endothelial damage through T-cell and cytokine-mediated injury.<sup>73</sup> Gastrointestinal mucosal involvement by GVHD contributes to prerenal acute kidney injury through poor fluid intake and excessive gastrointestinal losses. The sinusoidal obstruction syndrome, an independent risk factor for acute kidney injury, clinically mimics the hepatorenal syndrome because of the associated acute portal hypertension that develops from hepatic sinusoidal injury.<sup>70,73,74</sup> Patients with hematopoietic stem-cell transplants are often prescribed medications such as vancomycin, aminoglycosides, acyclovir, and amphotericin, which can cause acute kidney injury through mechanisms such as direct nephrotoxicity and tubulointerstitial nephritis.<sup>70,73,74</sup> Calcineurin inhibitors can also cause hemodynamic acute kidney injury and have been associated with the development of thrombotic microangiopathy.<sup>70,73,74</sup> In addition, viral infections — in particular, adenovirus, BK virus, and cytomegalovirus infections — are associated with acute kidney injury (tubulointerstitial nephritis and glomerulonephritis).

#### CHEMOTHERAPY-INDUCED ACUTE KIDNEY INJURY

Traditional chemotherapeutic agents, newer targeted therapies, and evolving immunotherapies are extending the lives of patients with malignant disease. Unfortunately, acute kidney injury remains an important and growing complication of drug therapy in patients with cancer.<sup>75,76</sup> Table 3 lists commonly used drugs, their mechanisms of action, associated renal histopathological features, and resulting clinical nephrotoxic effects.

A number of conventional chemotherapeutic agents cause acute kidney injury.<sup>75-77</sup> These drugs may injure the renal microvasculature, glomeru-

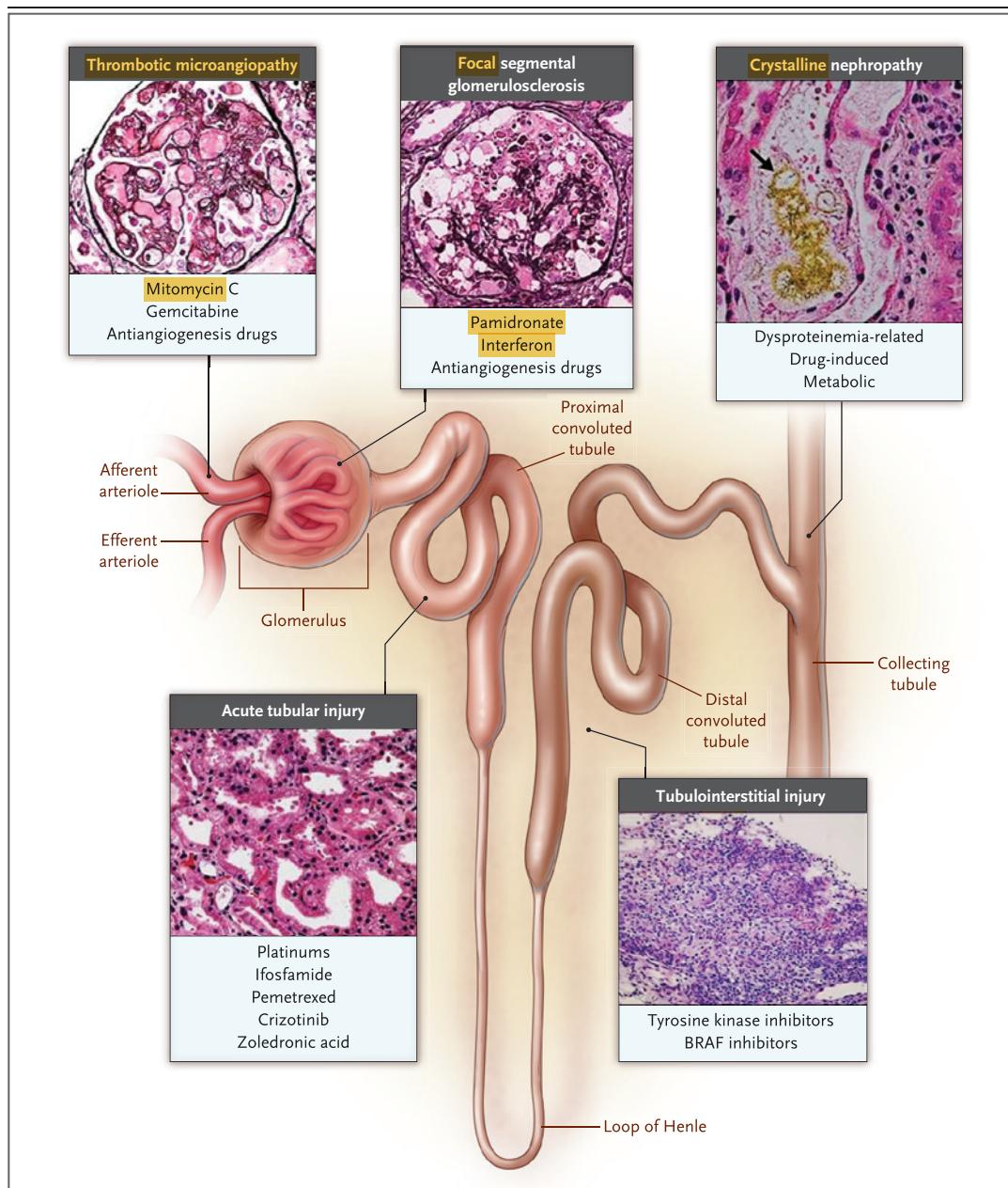
**Table 3. Common Anticancer Drugs Associated with Acute Kidney Injury.\***

Medication	Mechanism of Action	Renal Histopathological Features	Clinical Nephrotoxic Effects
<b>Chemotherapeutic agents</b>			
Cisplatin†	Cross-linking and interference with DNA replication	Acute tubular injury and acute tubular necrosis	Acute kidney injury, proximal tubulopathy, Fanconi's syndrome, NDI, sodium and magnesium wasting
Ifosfamide	Nitrogen mustard alkylating agent; inhibition of DNA synthesis through DNA strand-breaking effects	Acute tubular injury and acute tubular necrosis	Acute kidney injury, proximal tubulopathy, Fanconi's syndrome, NDI
Pemetrexed	Antifolate agent; inhibition of dihydrofolate reductase, thymidylate synthase, and glycinamide ribonucleotide formyltransferase	Acute tubular injury and acute tubular necrosis	Acute kidney injury, proximal tubulopathy, Fanconi's syndrome, NDI
<b>Methotrexate</b>	Antifolate agent; inhibition of dihydrofolate reductase	<b>Crystalline nephropathy</b> and acute tubular injury	Acute kidney injury
<b>Pamidronate</b>	Pyrophosphate analogue; associated with moderate FPPS inhibition	Focal segmental glomerulosclerosis, acute tubular injury	Nephrotic syndrome, acute kidney injury
<b>Zoledronic acid</b>	Pyrophosphate analogue; associated with potent FPPS inhibition	Acute tubular injury and acute tubular necrosis	Acute kidney injury
<b>Targeted agents</b>			
Anti-VEGF drugs	VEGF-receptor antibody or soluble receptor; inhibition of VEGF signaling	Thrombotic microangiopathy	Acute kidney injury, proteinuria, hypertension
Tyrosine kinase or multikinase inhibitors (sunitinib, sorafenib, pazopanib)	Inhibition of tyrosine kinase or multikinase signaling, with activity against RAF kinase and several receptor tyrosine kinases (e.g., VEGF, PDGF)	Thrombotic microangiopathy, focal segmental glomerulosclerosis, tubulointerstitial nephritis	Acute kidney injury, proteinuria, hypertension
BRAF inhibitors (vemurafenib and dabrafenib)	Inhibition of the mutated BRAF V600E kinase that leads to reduced signaling through the aberrant MAPK pathway	Acute tubular injury, tubulointerstitial nephritis	Acute kidney injury, electrolyte disorders
ALK inhibitors (crizotinib)	Inhibition of the mutated anaplastic lymphoma kinase	Acute tubular injury, tubulointerstitial nephritis	Acute kidney injury, electrolyte disorders, renal microcysts
<b>Immunotherapeutic agents</b>			
Interferons	Activation of STATs, which are transcription factors that regulate immune system gene expression	Thrombotic microangiopathy, focal segmental glomerulosclerosis	Acute kidney injury, nephrotic proteinuria
CTLA-4 inhibitors	T-cell activation by antibody blocking CTLA-4 receptor	Tubulointerstitial nephritis, lupuslike glomerulonephritis‡	Acute kidney injury, proteinuria
PD-1 inhibitors	T-cell activation by antibody blocking PD-1 receptor	Tubulointerstitial nephritis‡	Acute kidney injury
<b>Chimeric</b> antigen receptor T cells	T-cell targeting of specific tumor-cell antigens	No pathological features described	Capillary leak syndrome with prerenal acute kidney injury

\* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, FPPS farnesyl pyrophosphate synthase, MAPK mitogen-activated protein kinase, NDI nephrogenic diabetes insipidus, PD-1 programmed death 1, PDGF platelet-derived growth factor, STAT signal transducer and activator of transcription, and VEGF vascular endothelial growth factor.

† Carboplatin and oxaliplatin are less nephrotoxic than cisplatin.

‡ In some cases, tubulointerstitial nephritis is accompanied by granulomatous interstitial nephritis.



**Figure 2. Anticancer Therapies and Their Site of Action in the Nephron.**

Drugs used to treat cancer can cause various forms of injury in sites in the nephron such as the arterioles, glomerulus, tubules, and interstitium. In the image of crystalline nephropathy, the arrow points to methotrexate crystals. The stains are Jones methenamine silver (thrombotic microangiopathy and focal segmental glomerulosclerosis images), hematoxylin and eosin (crystalline nephropathy and acute tubular injury images), and periodic acid–Schiff (tubulointerstitial injury image). BRAF denotes serine–threonine protein kinase.

lus, tubular segments, and renal interstitium (Fig. 2). Clinical renal syndromes that develop with these drugs include acute kidney injury, proteinuria–hematuria, the nephrotic syndrome, isolated tubulopathies (with accompanying elec-

trolyte and acid–base disturbances), hypertension, and chronic kidney disease.<sup>75</sup> Thrombotic microangiopathy, which has been reported in association with gemcitabine or mitomycin C therapy, may cause endothelial injury in the renal

microvasculature.<sup>78,79</sup> Focal and segmental glomerulosclerosis and minimal change disease, along with acute tubular injury, complicate pamidronate therapy by damaging the glomerular (and tubular) epithelium, which promotes a form of drug-induced podocytopathy.<sup>75,77</sup> Most common is acute tubular injury or necrosis due to treatment with platinum-containing regimens, ifosfamide, zoledronic acid, pemetrexed, and numerous other chemotherapeutic agents.<sup>75,76</sup> These drugs can induce direct cellular toxicity as a result of their transport through tubular cells, induction of mitochondrial injury, oxidative stress, and activation of apoptotic signaling pathways within cells.<sup>75,76</sup>

There are no well-established therapies to treat these forms of acute kidney injury, apart from drug discontinuation and supportive measures. Other drug-induced forms of acute kidney injury include obstructive and inflammatory interstitial injury resulting from intratubular crystal precipitation induced by methotrexate and interstitial nephritis from various chemotherapeutic agents, such as ifosfamide, carboplatin, and doxorubicin.<sup>75,76</sup>

Targeted agents, defined as drugs designed to target specific gene mutations in malignant tissue, inhibit oncogenic signaling cascades associated with tumor growth. These agents, which are effective in the treatment of several cancers,<sup>78</sup> have become a prominent cause of acute kidney injury. As with chemotherapeutic drugs, targeted agents cause injury in all nephron segments. Acute kidney injury, low-grade and nephrotic proteinuria, hypertension, and electrolyte disturbances are observed with many of these drugs. Vascular injury and glomerular injury occur with antiangiogenesis drugs targeting vascular endothelial growth factor.<sup>78,79</sup> Although a number of lesions have been described in association with these drugs, thrombotic microangiopathy (associated with agents targeting vascular endothelial growth factor) and focal segmental glomerulosclerosis (associated with tyrosine kinase inhibitors) are the most common and are frequently associated with acute kidney injury.<sup>79</sup>

Therapy with the BRAF (serine–threonine protein kinase) inhibitors, vemurafenib and dabrafenib, is complicated by a dose-related acute kidney injury, which appears to be due to acute tubulointerstitial injury, although the histologic data available in these cases are limited.<sup>80</sup> The

mechanism of kidney injury with BRAF inhibitors is unknown but may involve interference with the downstream mitogen-activated protein kinase pathway, which increases renal susceptibility to ischemic tubular injury. Drug discontinuation is associated with reversal of acute kidney injury in approximately 80% of cases.<sup>80</sup> The anaplastic lymphoma kinase 1 inhibitor, crizotinib, causes acute kidney injury through tubular injury and is associated with renal cyst formation, as well as electrolyte disturbances in rare cases.<sup>81,82</sup>

Immunotherapy, such as treatment with interferon and high-dose interleukin-2, as well as drugs that stimulate the host's immune system to destroy cancer cells, such as checkpoint inhibitors and chimeric antigen receptor T cells,<sup>83-87</sup> may also cause acute kidney injury. Interferon is associated with high-grade proteinuria, acute kidney injury, and evidence of glomerulopathies — minimal change disease and focal segmental glomerulosclerosis — on kidney biopsy.<sup>84</sup> Interferon-related glomerular injury may be due to direct binding of interferon to podocyte receptors and alteration of normal cellular proliferation.<sup>87</sup> Macrophage activation and skewing of the cytokine profile toward interleukin-6 and interleukin-13, which may affect permeability in podocytopathies, are also possible mechanisms.<sup>84</sup> Drug discontinuation (with or without glucocorticoid therapy) is effective in reversing acute kidney injury and proteinuria in patients who have minimal change disease but is less effective in those with focal segmental glomerulosclerosis, especially collapsing focal segmental glomerulosclerosis.<sup>84</sup>

The checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab activate host T cells to enhance tumor killing by preventing tumor ligand binding to cytotoxic T-lymphocyte antigen 4 and programmed death 1 receptors, which deactivate T cells. However, this effect causes loss of self-tolerance (and perhaps tolerance of other drugs), leading to various forms of autoimmune injury, including acute interstitial nephritis, which is associated with moderate-to-advanced-stage acute kidney injury.<sup>85,86</sup> Glucocorticoid therapy and drug discontinuation generally reverse acute kidney injury due to treatment with checkpoint inhibitors.<sup>85,86</sup> Chimeric antigen receptor T cells are engineered to express receptors that recognize and bind tumor antigens, ultimately

directly targeting and destroying cancer cells. Such therapy, however, may be complicated by the cytokine release syndrome, which can result in capillary leak and prerenal azotemia.<sup>87</sup>

TREATMENT DECISIONS  
FOR PATIENTS WITH CANCER  
AND ACUTE KIDNEY INJURY

Both the short-term and long-term outcomes of acute kidney injury in patients with cancer are poor, with one study showing a 60-day survival rate of only 14%.<sup>88</sup> However, selected patients can benefit from aggressive care; thus, decisions regarding the initiation of dialysis are complex and require input from the entire care team to assess the reversibility of the acute injury, the longer-term cancer prognosis, and the quality of

life before the acute injury.<sup>89</sup> Furthermore, the patient's preferences must be considered in the decision regarding dialysis initiation. The process of shared decision-making is recommended for working through the issues regarding dialysis initiation in these complex situations.<sup>90</sup>

SUMMARY

Acute kidney injury in patients with cancer has diverse causes and negative outcomes. Efforts to prevent acute kidney injury in this patient population are likely to improve outcomes and allow patients to reap the benefits of advances in cancer treatments.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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