CHAPTER 41

Acute Kidney Injury in Oncology and Tumor Lysis Syndrome

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OBJECTIVES

This chapter will:

1. Review the epidemiology and causes of acute renal failure in cancer patients.
2. Highlight the pathophysiologic mechanisms of acute nephrotoxicity in cancer patients treated with traditional cytotoxic chemotherapy or novel agents.
3. Describe the pathogenesis of acute renal failure in specific settings such as myeloma, high-dose chemotherapy/bone marrow transplantation, and tumor lysis syndrome.
4. Summarize recommendations on how to prevent acute renal failure in cancer patients and how to treat the condition when it develops.

The presence of acute kidney injury (AKI) is probably the most common form of renal disease for which a nephrologist would be consulted in hospitalized cancer patients, leading to a number of negative consequences relative to patients' care, including length of hospitalization, denial of active cancer treatment, worsening of overall prognosis, and last but not least, increase in costs. Furthermore, oncologic patients have an increased risk of developing AKI within the first year from the diagnosis of cancer, and this combination negatively affects their survival; this is particularly true for the elderly, who have the highest cancer incidence rates and 10-fold higher AKI rates compared with the non-elderly population.[1]

Most concerning is the increased mortality noted in cancer patients who have developed AKI in addition to a

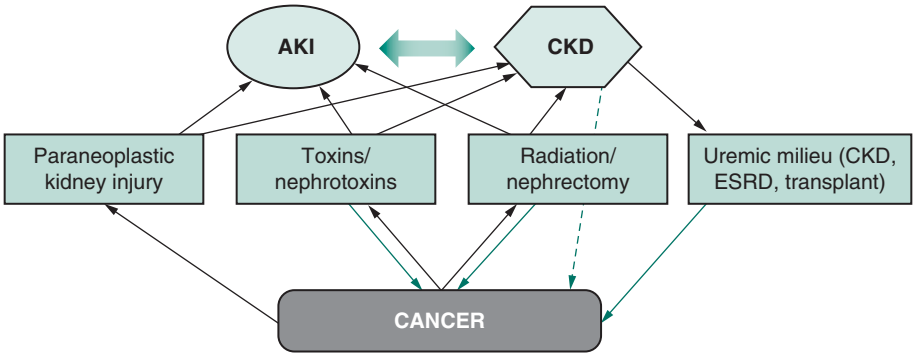

FIGURE 41.1 The "circular" relationship existing between acute kidney injury, chronic kidney disease, and cancer.

preexisting chronic kidney disease (CKD), as compared with those without kidney disease. Furthermore, the relationship between kidney disease and cancer has been defined as "circular."[2] Indeed, AKI may disturb the bioavailability and/or safety profile of certain oncologic drugs, potentially leading to suboptimal treatments, or enhanced risk for drug-induced de novo kidney injury or worsening of preexisting CKD. Finally, some very effective anticancer agents may be avoided as a potential option in patients with AKI because of the lack of specific information on their pharmacokinetic properties in this setting.[2]

Cancer, AKI, and CKD are closely linked as shown in Fig. 41.1.

The growing prevalence of cancer and AKI implies that an increasing number of patients will require the expertise of an onconephrologist, who must be knowledgeable about the possible causes of AKI in cancer patients, the pharmacokinetics of oncologic agents in patients with AKI (and CKD), and their potential toxic effects on kidney function.[2]

EPIDEMIOLOGY AND RISK FACTORS

The largest study addressing the bulk of AKI in cancer patients is a Danish population study[1] in which 1.2 million people were followed from 1999 to 2006. During the whole observation period, more than 37,000 incident cancers occurred. The 1-year risk of AKI, defined by the RIFLE (Risk, Injury, Failure, Loss, End-Stage) criteria, in this population was 17.5%, with a 27% risk over 5 years. The most common malignancies in which AKI was observed were renal cell cancer (44%), multiple myeloma (33%), liver cancer (32%), and leukemia (28%).

Notably, patients with metastatic disease were at the highest risk of developing AKI. Moreover, more severe AKI, defined as a doubling of serum creatinine, had an 8.8% and 14.6% risk at 1 and 5 years, respectively. Even more severe AKI (corresponding to failure in RIFLE criteria and reflecting a tripling of serum creatinine or absolute rise >4 mg/dL) was seen in 4.5% and 7.6% of patients at 1 and 5 years, respectively. Among cancer patients with any stage of AKI (9613 total), 5.1% required dialysis within 1 year of AKI onset. Notably enough, the 28-day mortality of cancer patients who require dialysis has been estimated to be 66% to 88%.[3]

Several risk factors for the development of AKI in cancer patients have been identified for solid and hematologic malignancies; these factors are reported in Table 41.1.

TABLE 41.1

Risk Factors of Acute Kidney Injury in Patients With Hematologic Malignancies and Solid Tumors

Hematologic Malignancies	Solid Tumors
Age > 65 years	
Congestive heart failure (primitive or caused by oncologic treatments)	
Chronic kidney disease (primitive or caused by oncologic treatments)	
Volume depletion (hypovolemia, hypotension, dehydration resulting from vomiting, diarrhea, stomatitis, etc.)	
Sepsis (often central vascular device-related)	
Myeloma	Nephrectomy for renal cell carcinoma
Leukemia and lymphoma	Hepatocellular carcinoma and cholangiocarcinoma

TABLE 41.2

Main Causes of Acute Kidney Injury in Patients With Hematologic Malignancies and Solid Tumors

Hematologic Malignancies	Solid Tumors
Prerenal	
Nausea, vomiting, and diarrhea	
Stomatitis and cachexia	
"Third spacing" (including hepatorenal syndrome)	
Sepsis	
Hepatic venoocclusive disease (VOD)	
Capillary leak syndrome (IL-2)	
Renal	
Antineoplastic agents (either cytotoxics or targeted agents)	
Contrast medium	
Bisphosphonates	
Nonsteroidal antiinflammatory drugs	
Thrombotic microangiopathies	
Paraneoplastic glomerulonephritis	
Immunomediated nephritis	
Tumor lysis syndrome	
(less common in solid tumors)	
Light chain–associated glomerular disease	
Cancer infiltration	
Postrenal	
Compression/obstruction (tumor-related or radiotherapy-related)	

Beyond risk factors, several tumor-specific causes of AKI have been evidenced, which are reported in Table 41.2.

ACUTE KIDNEY INJURY IN SOLID TUMORS

The most common cause of AKI in patients affected by solid tumors is represented by cancer treatment; cytotoxic chemotherapy, as well as novel targeted agents, are often nephrotoxic and account for the vast majority of cases of kidney injury in these patients.

Acute Nephrotoxicity From Cytotoxic Chemotherapy

Currently, the cytotoxic chemotherapeutic agents most commonly responsible for the development of AKI are cisplatin (CDDP), mitomycin-C (MM-C), gemcitabine, methotrexate (MTX), ifosfamide, and pemetrexed.

Cisplatin

CDDP (cis-dichlorodiammineplatinum) is one of the most commonly used cytotoxic agents, used as a monotherapy or in combination with other agents, to treat a wide spectrum of tumors, such as lung, ovarian, head and neck, bladder, cervical, and testicular cancers.

CDDP-induced nephrotoxicity is multifactorial.[4] CDDP induces the production of reactive oxygen species (ROS) and inhibits several antioxidant enzymes, leading to massive oxidative stress injury. Furthermore, it increases renal expression of tumor necrosis factor-alpha, leading to increased tubular cell apoptosis. Cisplatin is excreted and concentrated in the kidneys entering renal tubular cells via the organic cation transporter-2 (OCT-2), which is kidney specific.

Renal injury from CDDP is dose dependent and is first characterized by a decrease in renal blood flow leading to a decline in eGFR within 3 hours of CDDP administration; these changes probably are due to increased vascular resistance secondary to tubuloglomerular feedback and increased sodium chloride delivery to macula densa.[4]

Acute tubular toxicity of CDDP causes mitochondrial dysfunction, decreased ATPase activity, impaired solute transport, and altered cation balance. As a result, sodium and water reabsorption is decreased, and salt and water excretion are increased, often leading to polyuria.[4] CDDP also causes dose-dependent renal magnesium wasting.

Tubulointerstitial injury is a predominant finding on pathologic examination; both proximal and distal tubules are affected. Acute tubular necrosis is the main finding in patients who developed CDDP-induced AKI.

Patients with CDDP toxicity typically have progressive azotemia in the setting of bland urinalysis and minimal proteinuria. Although renal function improves in most patients, a subgroup of patients developed irreversible renal impairment. Hypomagnesemia is common and is observed in more than half of the patients, depending on total CDDP dose and length of exposure.

Renal salt-wasting syndrome has been reported in up to 10% of patients, occurring as hyponatremia and severe orthostatic hypotension in the setting of high urinary sodium concentration. Rare cases of thrombotic microangiopathies (TMAs) have been reported in patients treated with CDDP, especially when coadministered with other agents. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been documented in patients receiving vigorous hydration but is less common now because cisplatin-associated nausea is treated with new-generation antiemetics, diminishing the stimulus for antidiuretic hormone secretion.

Often AKI in CDDP-treated patients is caused by indirect toxicities, such as nausea and vomiting, leading to volume depletion.

Hyperhydration has been shown to reduce the incidence of AKI in patients receiving CDDP, whereas there is no evidence of benefit from mannitol and loop diuretics, although they often are used by oncologists. Numerous compounds have been proposed to prevent cisplatin nephrotoxicity, but only amifostine has been approved by U.S. Food and Drug Administration (FDA) for protection against cumulative nephrotoxicity from CDDP therapy. Amifostine is protective by increasing the binding of ROS to thiol groups. Side effects, cost, and concerns that it also diminishes antitumor effect have limited its use in clinical practice. A recent study in a murine model showed that magnesium supplementation during cisplatin therapy may attenuate renal damage; however, further studies in humans are needed to validate these findings.

Mitomycin-C

Mitomycin-C (MM-C) is an antitumor antibiotic isolated from *Streptomyces caespitosus* used for the treatment of gastrointestinal (GI) and other solid tumors. MMC-C-induced toxicity is often associated with pulmonary and neurologic manifestations and can be life threatening. Long-term treatment with MM-C can lead to progressive renal insufficiency and subacute renal failure and has been associated with TMAs. Kidney pathophysiologic changes observed in patients developing MM-C–induced TMA are due to the direct toxic effects of the oncologic agent on the endothelium. Patients experience gradual onset of anemia and thrombocytopenia, with high lactate dehydrogenase (LDH) levels and undetectable haptoglobin levels; progressive renal insufficiency is accompanied by increasing blood urea nitrogen (BUN) and creatinine levels, as well as severe hypertension. The urinalysis shows microhematuria and proteinuria.

MM-C nephrotoxicity is dose dependent, with the risk of TMA being 1.6% with cumulative doses above 40 mg/m^2 and as high as 30% at doses exceeding 70 mg/m^2.

Therefore doses exceeding 40 mg/m^2 should be avoided.

Current practice restricts MM-C treatment to 2 to 3 months. Nevertheless, some patients are still seen who have received MM-C for a longer period of time, and these usually demonstrate a slow rise in BUN and creatinine levels, hypertension, thrombocytopenia, and anemia.

Gemcitabine

Gemcitabine is a pyrimidine analogue used in the treatment of a variety of solid tumors. Nephrotoxicity of this agent usually manifests as an overt TMA.[5] During early clinical development, TMA was reported at an extremely low rate of 0.015%; however, as the drug became more widely used, the incidence increased to as high as 2.2%. TMA presents as new-onset renal insufficiency, various degrees of microangiopathic hemolytic anemia (MAHA), and new or worsening hypertension. No clear-cut relationship has been established between the cumulative dose of gemcitabine and risk of TMA. Notably, the hematologic abnormalities often regress spontaneously, and renal function also may improve over time.[5]

In a single institution experience of 29 cases of gemcitabine-induced TMA, de novo renal dysfunction or worsening of preexisting CKD was recorded in all patients; kidney biopsies were performed in four cases and showed the presence of thrombi in small blood vessels, glomerular mesangiolysis, and widening of subendothelial space with detachment of endothelial cells from the glomerular basement membrane.[5] In this study, the development of TMA was independent of cumulative dose, which ranged from 4 to 81 g/m^2. After discontinuation of gemcitabine, 28% of patients had complete recovery of renal function, and 48% had partial recovery, or stable renal function. Although patients in this study did not undergo plasmapheresis, some authors advocated this treatment for patients with gemcitabine-induced TMA. Literature reviews show no difference in outcomes between patients treated with plasmapheresis and conservative management with drug withdrawal.[5] Eculizumab, a monoclonal antibody directed against the complement protein C5, already approved for treatment of atypical hemolytic uremic syndrome (HUS), has been used to treat gemcitabine-induced TMA.[6] Of six patients reported in the literature, two had complete renal recovery, two had partial improvement in renal function, and the remaining two showed no improvement. Given the response rates similar to supportive care alone, the use of eculizumab should be weighed carefully against its high cost.

Methotrexate

Methotrexate (MTX) is an antifolate agent that inhibits dihydrofolate reductase (DHFR), an important step in DNA synthesis. Between 50% and 70% of the drug is bound to plasma proteins, and 95% is found in the urine 30 hours after administration in subjects with normal renal function. MTX is filtered and secreted by the kidneys. It is a weak organic acid and is poorly soluble in acidic urine. Although it is administered over a large therapeutic range, only high-dose methotrexate (HD-MTX) (i.e., MTX given at doses >1 g/m^2) has the potential for becoming nephrotoxic. MTX renal toxicity is presumed to be due to direct precipitation of the drug, as well as to direct toxic effects on renal tubules. In a large clinical trial of 3887 patients treated with HD-MTX, renal dysfunction occurred in 1.8% of the subjects and was associated with a 4.4% mortality.[7] Affected patients usually develop nonoliguric or, in more severe cases, oliguric AKI shortly after the administration of HD-MTX. Urinalysis is generally bland and shows no proteinuria. Because MTX is excreted in the urine, renal impairment affects the clearance of the drug. Prolonged exposure to toxic levels of MTX (>10 mmol/L at 24 hours; >1 m mol/L at 48 hours, and >0.1 m mol/L at 72 hours) may lead to life-threatening nonrenal toxicities such as prolonged cytopenias, mucositis, neurotoxicity, and hepatic dysfunction. MTX solubility is 10-fold higher in urine with a pH of 7.5 than in acidic urine, and therefore urinary alkalinization and aggressive hydration (2.5–3.5 L/m^2 per 24 hours, starting 12 hours before chemotherapy administration) are important steps to establish brisk diuresis and prevent MTX precipitation in the tubules. Probenecid, penicillins, salicylates, and nonsteroidal antiinflammatory drugs may increase the risk of nephrotoxicity because they interfere with renal tubular secretion of MTX and delay its excretion. Prevention of nephrotoxicity, together with MTX titers monitoring, is crucial to prevent extrarenal MTX toxicity. Leucovorin rescue is used in patients who develop nephrotoxicity and is aimed at prevention of nonrenal complications. Leucovorin acts as an antidote by bypassing blocked DHFR pathway. In patients who have toxic levels of MTX, leucovorin rescue is given according to established nomograms, with doses of 100 to 1000 mg/m^2 administered every 6 hours. Leucovorin rescue is the only therapy that proved to be useful in patients with MTX toxicity. Hemodialysis and hemoperfusion have been used in an attempt to remove MTX from circulation. Although both modalities result in lower MTX plasma levels immediately after treatment, there is a significant rebound effect with levels reaching 90% to 100% of preprocedure MTX concentrations. Because MTX is highly protein bound, regular dialysis will not clear the drug efficiently, and high doses of leucovorin are needed to prevent systemic toxicity. Glucarpidase (carboxypeptidase-G2), a recombinant bacterial enzyme that rapidly metabolizes MTX to inactive compounds, is able to decrease MTX plasma level more than 98% within 15 minutes after administration and is effective as a single dose. MTX concentration rebounds occurred in 60% of the patients, usually with an increase no greater than 10% in plasma MTX concentrations.

Time to renal recovery in most glucarpidase studies was similar to that of observed with leucovorin rescue. In one study, glucarpidase was associated with lower risk of grade 4 nonrenal toxicity if administered less than 96 hours after HD-MTX. However, in the same study, inadequate leucovorin rescue was predictive of nonrenal toxicities. Glucarpidase affects only extracellular levels of MTX, which may explain the delay in renal recovery after MTX removal from circulation. Carboxypeptidase-G2 and high-dose leucovorin have been tested in patients with MTX intoxication and AKI, with similar results.

Rescue with leucovorin (50 mg four times a day) should be started 24 hours after completion of each HD-MTX infusion, and serum MTX concentrations should be measured daily.

Unless such agents are absolutely necessary, patients should not be given medications that inhibit folate metabolism (e.g., trimethoprim-sulfamethoxazole), exhibit intrinsic renal toxicity (e.g., nonsteroidal antiinflammatory agents, contrast agents), or decrease the fraction of MTX bound to albumin (e.g., aspirin).

Ifosfamide

Ifosfamide is an alkylating agent used in the treatment of a variety of childhood and adult malignancies. Its use, however, is associated with a significant risk for nephrotoxicity. Because it is used commonly in children, most of the data pertaining to nephrotoxicity of ifosfamide have been obtained in pediatric patients. It has been reported that estimated Glomerular Filtration Rate (eGFR) is less than 90 mL/min/1.73 m^2 in 50% of and less than 60 mL/min/1.73 m^2 in 11% of patients treated with ifosfamide, with an average reduction of eGFR of 35.1 mL/min/1.73 m^2 at a median of 6 months after treatment. In adults, ifosfamide has been shown to reduce mean eGFR from 81.5 to 68.5 mL/min/1.73 m^2 1 year after treatment in patients with prior exposure to CDDP. Fanconi syndrome, characterized by proximal tubular dysfunction with variable degrees of glucosuria in the setting of normoglycemia, renal phosphate and potassium wasting, proximal tubular acidosis, hypouricemia, and aminoaciduria, has been reported in 5% of patients treated with ifosfamide.[8] Patients who receive cumulative doses of less than 60 g/m^2 are at lower risk of renal toxicity, whereas patients receiving more than 100 g/m^2 are at highest. Platinum combination therapy, nephrectomy, and hydronephrosis are additional risk factors. Renal disease may progress even after ifosfamide is discontinued and

may lead to end-stage renal disease (ESRD). Although the precise incidence of severe kidney dysfunction after ifosfamide exposure is unknown, a recent review[8a] indicates that it appears to be a sporadic complication without clear relationship to cumulative dose.

Pemetrexed

Pemetrexed is an antifolate agent that inhibits several enzymes involved in DNA synthesis. This drug is not metabolized significantly, and 70% to 90% of the drug is excreted unchanged in the urine within the first 24 hours after administration. The half-life of pemetrexed is 3½ hours in patients with normal renal function but is increased in patients with renal insufficiency resulting in higher exposure to the drug. Pemetrexed has not been studied in patients with eGFR less than 45 mL/min/1.73 m^2, but a fatality was reported in a patient with an eGFR of 19 mL/min/1.73 m^2 who received this drug. Mild and reversible renal toxicity has been reported in patients who received high-dose therapy (>600 mg/m^2). Recently, several cases of pemetrexed-induced tubular injury[9] were reported, including interstitial nephritis and fibrosis, as well as diabetes insipidus. After discontinuation of pemetrexed, the renal function stabilized in the majority of patients, but never returned to baseline levels.

Acute Nephrotoxicity From Targeted Therapies

As a whole, the term *targeted therapies* encompasses a huge number of anticancer agents used to treat a number of different tumor types. Although clearly effective, these drugs have well-described dose-dependent adverse renal effects. Hypertension and proteinuria often are seen, but nephrotic-range proteinuria and/or AKI also may develop. As a whole, targeted agents–induced AKI is definitely less frequently observed, as compared with that related to the use of cytotoxic chemotherapy, and often has a multifactorial genesis. Notably enough, in registrative studies of targeted agents, too often kidney impairment is mentioned just as "creatinine increase" without any insight in the real nature of kidney injury.[2]

The underlying pathophysiologic changes that lead to the various kidney lesions are not definitely known but are related primarily to downstream effects of antivascular endothelial growth factor (anti-VEGF) effects on the glomeruli. A meta-analysis demonstrated that bevacizumab therapy resulted in overt proteinuria (>0.5 g/day) in 21% to 41% of patients treated with low-dose (5–7.5 mg/kg) drug (relative risk for proteinuria, 1.4) and up to 64% (relative risk for proteinuria, 2.2) in the high-dose (15 mg/kg) group.[2]

Hypertension also developed in a dose-related manner with this drug: at low dose the relative risk for hypertension was 3.0, and at high dose the relative risk for hypertension was 7.5.

The kidney lesions observed with these drugs include glomerular endotheliosis, focal segmental glomerulosclerosis (sometimes collapsing), various glomerulopathies, and most commonly TMA with a few cases of acute interstitial nephritis.[2,10] TMA related to VEGF/VEGF receptors (VEGFRs) inhibitors were localized primarily to the kidney, and only half of the patients experienced thrombocytopenia or schistocytosis.

TMA induced by gemcitabine, CDDP, and/or MM-C is more aggressive, has greater hematologic abnormalities, glomerular and arteriolar renal localization, extrarenal symptoms, and worse renal survival despite drug discontinuation, as compared with anti-VEGF/VEGFRs-induced TMA, which often present just with renal involvement. Thus nephrologists should be aware of these clinical manifestations when asked to consult on these patients. In general, hypertension and proteinuria should prompt blood pressure–lowering therapy but not drug discontinuation.[2] In contrast, AKI with TMA is an indication to interrupt drug therapy. Although there are no published guidelines, patients receiving these drugs should be monitored with blood pressure surveillance, as well as with intermittent kidney function and proteinuria surveillance, to identify these complications early.

ACUTE KIDNEY INJURY IN HEMATOLOGIC MALIGNANCIES

AKI often is found in patients with hematologic malignancies (i.e., leukemia, lymphomas, and, more commonly, multiple myeloma). Beyond direct involvement of the kidney, in leukemia and lymphoma patients, also lysozymuria and leukostasis may contribute to the development of AKI.

Acute Nephrotoxicity in Leukemia and Lymphoma

The development of kidney disease is common in patients with leukemia and lymphoma who are at risk for developing AKI from different causes: hypotension, sepsis, administration of radiocontrast, antifungal and antibacterial agents, cytotoxic chemotherapy, immunosuppressive drugs, hematopoietic stem cell transplantation (HSCT), or tumor lysis syndrome (TLS).

Renal involvement in leukemia and lymphoma is often an indolent and clinically silent disease, so patients can have slowly progressive CKD often attributed to other causes.[11] Patients may have AKI, but this is rare and is seen most commonly in highly aggressive and disseminated disease. Although uncommon, many cases of AKI attributable to leukemic infiltration of the kidney have been described. The real incidence of renal involvement in lymphomas is unknown, being usually clinically silent. Autopsy studies suggest that renal involvement occurs in about 90% of patients with lymphoma. Based on renal biopsy series from patients with lymphomas, patients who have AKI have predominantly bilateral interstitial infiltration of the kidneys by lymphoma cells and often have an increased renal size on radiographic imaging.[12] These findings suggest an increased interstitial pressure leading to a reduced intrarenal blood flow with subsequent renal tubular injury. In the presence of proteinuria, the local release of permeability factors and cytokines by lymphomatous cells has been suggested as its main pathophysiologic mechanism.

Regarding leukemia, autopsy studies have showed that 60% to 90% of patients with leukemia have renal involvement. On biopsy, cells usually are located in the renal interstitium, although occasional glomerular lesions are noted. As in the case of lymphomas, an increased interstitial pressure leads to vascular and tubular compression and subsequent tubular injury. Once again, most often kidney involvement is discovered incidentally at autopsy; renal enlargement on ultrasound (US) or computed tomography (CT) scan is its only overt manifestation.

Because it is so frequently silent from a clinical viewpoint, the diagnosis of AKI from leukemic or lymphomatous

infiltration of the kidney currently is based primarily on exclusion criteria.

As already highlighted, renal US or abdominal CT sometimes describes diffusely enlarged kidneys, sometimes with multiple focal lesions.[12] However, in a study of 668 consecutive patients with lymphoproliferative disease who underwent diagnostic imaging with a CT scan, only 3% to 5% were found to have kidney abnormalities.[12a] Because of increased metabolic activity within lymphomatous deposits, positron emission tomography (PET) may be more sensitive.

Although definitive diagnosis requires a renal biopsy, which is seldom feasible to contraindications, the following criteria should support the diagnosis: (1) presence of renal enlargement without obstruction, (2) absence of other causes of kidney disease, and (3) rapid improvement of kidney function after cytoreductive chemotherapy.

Indeed, the treatment of a lymphomatous or leukemic involvement of the kidney is directed at the underlying malignancy. In indolent malignant disease that can be managed by observation alone, the appearance of kidney involvement suggests the need for starting systemic therapy.

Lysozymuria

Lysozyme is a cationic protein produced by macrophages and monocytes and released in response to bacterial infection. It is freely filtered by the glomerulus and reabsorbed by the proximal tubule. In certain leukemias, clonal expansion leads to an excessive production of lysozyme and subsequent proximal tubular injury, ultimately resulting in AKI. Damage to the proximal tubule reduces reabsorption and may induce Fanconi syndrome and nephrotic range proteinuria. The presence of lysozymuria can be confirmed by detection of an increased globulin level on serum and urine protein electrophoresis with immunofixation negative for monoclonal gammopathy. Once again treatment is directed at the underlying malignancy.

Leukostasis

Patients with myeloid leukemia and exceedingly high white blood cell counts can develop organ dysfunction resulting from intravascular aggregation of leukemic cells. The pulmonary and cerebral circulations are those most commonly (and severely) affected, although there are case reports of patients developing AKI. In these cases, leukemic cells occlude the peritubular and glomerular capillaries, thereby reducing eGFR. Patients may be oliguric, but their renal function often improves with therapeutic leukapheresis and/or chemotherapy. Leukostasis is thought to result from the abnormal morphology of blast cells and the hyperviscosity of the serum.

Acute Nephrotoxicity in Multiple Myeloma

Multiple myeloma (MM) is characterized by the uncontrolled proliferation of a B cell clone. The aberrant B lymphocyte population secretes a paraprotein: either an intact monoclonal immunoglobulin or a derived fragment (usually a light chain fragment). Production of this nephrotoxic paraprotein by the abnormal B cells is responsible primarily for AKI in MM. The light chains normally are found together with heavy chains in the immunoglobulin molecule and are detected by urine protein electrophoresis and immunofixation. It is the second most common hematologic malignancy behind the heterogeneous family of non-Hodgkin lymphomas (NHL). Clinical symptoms are due to osteolysis of the bone, suppression of normal hematopoiesis, and the overproduction of monoclonal immunoglobulins that deposit in organ tissues, and include bone pain and fractures, anemia, infections, hypercalcemia, edema, heart failure, and renal disease.

Kidney Involvement and Pathology

More than one half of patients with MM initially have varying degrees of AKI.[13] Renal failure often anticipates the diagnosis of myeloma in half of those patients in whom renal dysfunction will occur and develops in most of the remaining patients within 1 month of the diagnosis of MM. Of the 50% of patients with MM who experience renal impairment, 10% require dialysis. AKI is associated with higher mortality, but this may be reflective of patients with more advanced disease.[13] AKI frequently is triggered by an event such as treatment with nonsteroidal antiinflammatory agents for pain control, use of intravenous (IV) contrast agents, development of hypercalcemia, volume depletion (diuretic treatment, septicemia), or cryoglobulinemia-associated renal failure. Furthermore, water, electrolyte, and acid-base disturbances are common in patients with MM; such abnormalities also may affect renal load.

The major diseases in the spectrum of myeloma-related kidney disease include cast nephropathy, light chain deposition disease (LCDD), and AL amyloidosis.[14] Renal biopsy demonstrates the presence of monotypic light chains on immunofluorescence exam, as well as characteristic ultrastructural features of deposits on electron microscopy. Less common forms of renal injury include light chain–induced Fanconi syndrome, cryoglobulinemia, proliferative glomerulonephritis, heavy chain deposition disease, and immunotactoid glomerulonephritis (Box 41.1).

Cast Nephropathy

Cast nephropathy has been diagnosed in 32% to 48% of patients with MM and renal disease.[15] Excess light chains precipitate with Tamm-Horsfall protein secreted by the thick ascending limb of the loop of Henle and produce casts in the distal tubule. Decreased eGFR may increase the concentration of light chains in the distal tubule and enhance the formation of casts. Therefore hypercalcemia, volume depletion, diuretics, and nonsteroidal antiinflammatory drugs can exacerbate renal injury. Renal injury is attributed to the direct toxic effects of urinary free light chains (FLC) on proximal

BOX 41.1

Kidney Manifestations of Multiple Myeloma

Myeloma cast nephropathy
Amyloid light chain (AL) amyloidosis
Light-chain deposition disease
Heavy-chain deposition disease
Immunotactoid glomerulopathy
Fibrillary glomerulopathy
Light-chain Fanconi syndrome
Plasma cells infiltration
Cryoglobulinemia
Membranoproliferative glomerulonephritis
Membranous glomerulonephritis

tubule cells. After reabsorption, lysosomal degradation of FLC can activate the nuclear factor (NF)-κB pathway leading to oxidative stress with an inflammatory response, apoptosis, and fibrosis. The classic presentation is an elderly patient with unexplained renal failure, anemia, and bone pain or fractures. Proteinuria, when quantitatively measured with a 24-hour urine collection, is usually subnephrotic and primarily composed of monoclonal light chains (Bence-Jones proteins). The qualitative measurement of proteinuria using a urine test strip, which mainly detects albumin, is generally minimally reactive. Most patients with MM cast nephropathy are diagnosed without kidney biopsy using serum and urine immunofixation and serum FLC analysis. LCDD has been diagnosed at autopsy in 19% of patients with MM and renal disease. The renal manifestations are most apparent clinically, whereas light chain deposits within the heart, liver, spleen, and peripheral nervous system may remain asymptomatic. Several retrospective reviews have reported on the clinical characteristics of these patients. The mean age was 58 years with no significant preference with respect to sex. Marked renal impairment was common on presentation, with a median serum creatinine above 4 mg/dL, and renal function rapidly declined thereafter. Nephrotic range proteinuria was detected in 26% to 40% of patients and correlated with the degree of glomerular involvement. Hypertension and microscopic hematuria also were present in the majority of patients. Therapy of LCDD is directed at the underlying hematologic malignancy, that is, MM. Advances in treatment of MM have made achieving remission fairly common, although relapses are unfortunately common.

The key to treating MM cast nephropathy is the rapid reduction in FLC concentrations. An early decrease in FLC levels is associated with the highest rate of renal recovery. In severe AKI resulting from cast nephropathy, a 60% reduction in FLC levels by day 21 after diagnosis is associated with renal recovery in 80% of cases. Previous studies with conventional chemotherapy protocols demonstrated that high-dose dexamethasone rapidly reduced FLC.[15]

HSCT is an important and potentially curative therapy in MM; however, patient selection criteria are stringent, and significant renal dysfunction traditionally has excluded patients from transplantation. Recent studies have shown that HSCT may be safe and effective in highly selected MM patients with renal failure.

Agents such as thalidomide and the proteasome inhibitor bortezomib also rapidly lower FLC concentrations; this has been referred to as "renoprotective chemotherapy." Significant improvement in renal dysfunction has been reported for MM patients treated with bortezomib-based regimens. Reversal of renal dysfunction with bortezomib may be more frequent and rapid than with other agents, based on observational analysis. Notably, no dose adjustments for renal function are necessary for bortezomib. Thalidomide and lenalidomide are two related immunomodulatory agents that are used commonly in the treatment of MM. Their effects likely are due to rapid lowering of serum FLC levels trough direct cell toxicity, inhibition of tumor cell growth factors, antiangiogenic activity, and increasing tumor immunity.

Lenalidomide dose must be adjusted for renal dysfunction, whereas thalidomide does not require dose adjustments. Regimens with thalidomide or lenalidomide have shown superior effectiveness as compared with traditional therapy with alkylating agents in terms of reversing renal dysfunction in MM; these agents may be nearly as effective as bortezomib regimens. Volume resuscitation to ensure optimum hemodynamic support and adequate urine output (3 L/day) are of critical importance in the initial management. The use of loop diuretics should be avoided unless there is volume overload. Hypercalcemia should be treated aggressively because it can lead to renal vasoconstriction, volume depletion, and enhanced cast formation. It has been suggested that urinary alkalinization decreases cast formation by reducing the net positive charge of FLCs and the interaction with THP. However, no clinical data support this approach. Given the risk of causing renal calcium precipitation in the setting of hypercalcemia, urinary alkalinization cannot be recommended.

Light chains are small-molecular-weight proteins; κ light chains usually circulate as monomers with a molecular weight of 22.5 kDa, whereas λ light chains are typically dimeric with a molecular weight of 45 kDa. Because of their size, there has been a keen interest in the use of extracorporeal therapies as a means of FLC removal, especially therapeutic plasma exchange and high cutoff hemodialysis.[15]

Therapeutic Plasma Exchange

Several small trials initially suggested that therapeutic plasma exchange (TPE) was effective in rapidly lowering FLC concentrations and improving renal function. However, these studies were small, usually monocentric, and underpowered. The largest randomized controlled trial of TPE did not demonstrate any benefit in patients with cast nephropathy. This study assessed the benefit of five to seven TPE sessions in 104 patients (30% required dialysis) with presumed cast nephropathy (not all patients had biopsy confirmation). There was no difference in the two groups with respect to the composite outcome of death, dialysis, and reduced renal function at 6 months. This lack of benefit may be related to the volume of distribution of FLC. Based on their molecular weights, 85% of light chains are confined to the extravascular space. Therefore a traditional 2-hour TPE session would be ineffective in removing significant amounts of FLC because of the excessive rebound effect. Most of the previous trials were performed before the availability of bortezomib-containing regimens. Although there is still interest in TPE as a therapy for cast nephropathy, its routine use cannot be recommended based on the current evidence.

High Cutoff Hemodialysis

More recently interest has developed for another method of extracorporeal removal of FLCs: high cutoff hemodialysis (HCO-HD). In this technique, a hemofilter with a large pore size (45 kDa) is used for extended periods of time to remove FLC. In the largest study of dialysis-dependent renal failure secondary to MM, 67 patients were treated with HCO-HD and chemotherapy (34). Only 57% of patients had a renal biopsy, of which 87% had cast nephropathy. Most patients (85%) received combination chemotherapy with dexamethasone and either bortezomib or thalidomide. The median number of HCO-HD sessions was 11, and all patients had extended (>4-hour) treatments. Overall, 63% of the patients became dialysis independent. The factors that predicted renal recovery were the degree of FLC reduction at days 12 and 21 and the time to initiating HCO-HD. Unfortunately, this trial did not have a control group to assess the benefit of HCO-HD compared with renoprotective chemotherapy alone. It is not known whether HCO-HD offers any additional benefit over current chemotherapeutic regimens. Randomized controlled trials proving the benefit of adding HCO-HD to patients with cast nephropathy treated with current chemotherapy will be necessary before its routine use can be recommended.

Amyloid light chain (AL) Amyloidosis

AL amyloidosis occurs when pathogenic light chains unfold and deposit as insoluble fibrils extracellularly within tissues. It is found in up to 15% of patients with MM on autopsy. In 40% of patients with AL amyloidosis, the bone marrow will have more than 10% plasma cells, although only 10% will meet other criteria for MM. Amyloid fibrils may deposit within any organ but most commonly affect the kidneys, heart, liver, and peripheral nervous system. Patients often experience fatigue, weight loss, and nephrotic syndrome. The clinical characteristics of patients with biopsy-proven renal amyloidosis were described in a retrospective review of 84 patients at the Mayo Clinic. The median age at diagnosis was 61 years, and 62% were male. The median serum creatinine on presentation was 1.1 mg/dL. The majority of patients had nephrotic syndrome (86%) with a median 24-hour protein loss of 7 g/day. Renal replacement therapy (RRT) was eventually required in 42% of patients, and median survival after starting dialysis was less than 1 year. In general, cardiac involvement occurs in nearly one third of patients and portends a poor prognosis. Treatment is targeted at decreasing the production of the amyloidogenic light chain.[16] Treatment with high-dose melphalan followed by HSCT increases hematologic response and overall median survival and currently offers the best chance for survival. Improvement in renal function highly correlates with increased survival.

ACUTE KIDNEY INJURY IN HEMATOPOIETIC STEM CELL TRANSPLANTATION

Acute kidney disease is common after HSCT and can lead to long-term effects. In addition, the occurrence of kidney disease in the setting of HSCT can affect negatively mortality and morbidity. The cause of HSCT-associated kidney injury is often multifactorial, including the direct toxicity of conditioning chemotherapy, the concomitant use of radiotherapy or of other nephrotoxic medications, the occurrence of sepsis, sinusoidal obstruction syndrome (SOS), transplantation-associated thrombotic microangiopathy (TA-TMA), and graft-versus-host disease (GVHD), not to take into account the possibility of a preexisting kidney disease.[17] The incidence of AKI varies, based on the definition of AKI, type of HSCT, and type of the chemotherapeutic conditioning regimen. When AKI is defined as a doubling of serum creatinine during the first 100 days after stem cell infusion, the prevalence ranges from 21% to 73%. Severity of AKI also varies. In a study of pediatric and adult allogeneic HSCT recipients, up to a third of all patients doubled their serum creatinine in the first 100 days, and 5% required acute dialysis.[18] Severity of AKI is associated with increased risk of morbidity and mortality.

For those receiving high-dose conditioning regimens and allogeneic HSCT, the incidence of AKI is as high as 69%. It often occurs before day +28 (day 0 representing the day of hematopoietic cell infusion), and risk factors include lung toxicity, hepatic toxicity, SOS, amphotericin exposure, and sepsis. For patients receiving reduced-intensity chemotherapy (RIC) and allogeneic HSCT, AKI occurs less frequently, later after transplant, and less often results in the need for dialysis. A retrospective cohort study found that 47% of RIC patients developed AKI compared with 73% in the high-dose treatment group, developing at a median of 26 to 60 days after transplant in the RIC group.[18a] Fewer RIC patients required dialysis, and mortality was significantly lower. Compared with allogeneic hematopoietic cell transplantation (HCT), AKI incidence is lower in autologous HSCT, occurring in approximately 21% of these patients. As a whole, AKI in the HSCT setting may be caused by the conditioning regimen, by prophylaxis for complications, or by other causes.

Causes of Acute Kidney Injury in the Hematopoietic Stem Cell Transplantation Setting: Conditioning Regimen

In allogenic HSCT, the infusion of donor hematopoietic cells is preceded by either myeloablative therapy (usually a combination of chemotherapeutic agents), with or without total body irradiation (TBI), or reduced-intensity (but still immunosuppressive) therapy that permits host hemopoietic cells to coexist with donor cells. All these treatments may lead to AKI; furthermore, AKI also may be caused by massive hemoglobinuria resulting from intravascular hemolysis secondary to use of dimethyl sulfoxide (DMSO) as a cryoprotectant, and release of free hemoglobin by red cells disrupted during the thawing of the graft. This complication has become infrequent because lower DMSO concentrations are now used and marrow grafts are "rinsed" after thawing and before infusion.

Causes of Acute Kidney Injury in the Hematopoietic Stem Cell Transplantation Setting: Prophylaxis for Complications

Allogenic graft recipients receive GVHD prophylaxis with immunosuppressive drugs (see Table 41.1). Prophylactic immunosuppression typically is continued until day +80.

Patients who develop acute GVHD (about 60%) are treated initially with high-dose prednisone. Those failing prednisone therapy are treated with more intense immunosuppressive agents, including anti T cell antibodies (antithymocyte globulin) and monoclonal antibodies (such as infliximab). Infection prophylaxis with antiviral, antibacterial, and antifungal agents represents an essential key of therapy in HCT setting. Notably calcineurin inhibitors (CNI) can lead to renal arteriolar vasoconstriction and have been associated with development of TA-TMA. In addition, the role of cyclosporine in the pathogenesis of AKI after allogeneic transplantation has been the subject of debate. The major dose-limiting toxicity of cyclosporine is nephrotoxicity, although the AKI it induces usually responds to dose reduction and is reversible on drug discontinuation. The risk of acute cyclosporine-related renal dysfunction generally correlates with plasma concentrations but notably is increased markedly by concomitant administration of other nephrotoxic drugs, especially amphotericin B. As a whole, medications commonly associated with AKI in the HSCT setting are reported in Table 41.3.

Causes of Acute Kidney Injury in the Hematopoietic Stem Cell Transplantation Setting: Other Causes

Other common risk factors potentially responsible for the development of AKI after HSCT include volume depletion, sepsis, exposure to nephrotoxic medications, SOS, and GVHD (Table 41.4).

TABLE 41.3

Medications Commonly Associated With Acute Kidney Injury in the Hemopoietic Stem Cell Transplantation Setting

Agents used within conditioning regimens	• Busulfan • Cyclophosphamide • Alemtuzumab • Cisplatin • Carboplatin • Amifostine • Vincristine • Lomustine (CCNU) • Radiation • Dimethyl sulfoxide (stem cell cryopreservative)
Antibacterial agents	• Aminoglycosides • Vancomycin • Trimethoprim/Sulfamethoxazole
Antiviral agents	• Cidofovir • Foscarnet • Acyclovir/ganciclovir • Immunoglobulin
Antifungal agents	• Amphotericin B • Caspofungin • Voriconazole
Agents used for the prophylaxis or treatment of GVHD	• Calcineurin inhibitors • Rapamycin • Methotrexate

GVHD, Graft-versus-host disease.

TABLE 41.4

Other Causes of Acute Kidney Injury in Hemopoietic Stem Cell Transplantation Setting

Intravascular volume depletion	Vomiting Diarrhea
Systemic vasodilatation	Sepsis
Renal vasoconstriction	Sinusoidal obstruction syndrome (SOS) Calcineurin inhibitors
Endothelial injury	Acute GVHD Calcineurin inhibitors Total body irradiation (TBI) Thrombotic microangiopathies (TMA)
Tubular injury	Other nephrotoxic medications Conditioning chemotherapy

GVHD, Graft-versus-host disease.

Owing to a propensity for increased GI fluid losses and poor oral intake, HSCT patients are highly susceptible to volume depletion. Close tracking of fluid intake, urine output, fluid losses via the GI tract and insensible losses, and daily weight measurement are thus mandatory. Additional measures that can discriminate prerenal AKI from other types include blood urea nitrogen/creatinine (BUN/Cr) ratio, fractional excretion of sodium (FENa), and fractional excretion of urea (FEurea). Sepsis can result in decreased effective circulating volume and hypotension and is a major risk factor for AKI. Sepsis-induced inflammation leads to increased capillary permeability and intravascular fluid leak, resulting in total body volume overload while depleting effective circulating volume and end organ perfusion. GVHD is unique to HSCT and likely causes tissue and endothelial damage via T cell– and cytokines-mediated injury. The GI mucosa is a common site of GVHD, contributing to inadequate fluid intake and increased GI losses. SOS and hepatorenal syndrome (HRS) have been identified as an independent risk factor for AKI.[19] Liver damage is a common complication of cytoreductive therapy and develops in 20% to 40% of bone marrow transplant recipients. The main site of liver damage in these patients is the hepatic sinusoid, and the resulting clinical syndrome thus is called SOS. Most cases of SOS are clinically obvious, with jaundice, liver pain, edema, and ascites. These clinical manifestations may be associated with AKI mimicking HRS, with normal histologic appearance of renal biopsy specimens. SOS can be classified as mild (i.e., clinically obvious, requires no treatment, and resolves completely), moderate (i.e., requires treatment but resolves completely), or severe (i.e., requires treatment but does not resolve before death or day 100). Severe SOS carries a dismal prognosis, with a 98% mortality rate in a cohort study.

AKI, as would be expected with any form of organ failure, influences the prognosis for SOS.[19] In patients with moderate SOS, diuretic therapy and analgesics are usually sufficient. In patients with severe SOS, treatment rests on supportive care. No satisfactory specific therapies are available. Defibrotide (a polydeoxyribonucleotide with antiischemic, antithrombotic, and thrombolytic properties) produced promising results in an open-label study but has not yet been investigated in randomized studies. Furthermore, thrombolytic therapy is of uncertain efficacy and carries a risk of fatal bleeding.

HRS results in decreased resistance in the systemic and splanchnic vasculature, leading to renal hypoperfusion and compensatory increase in renal salt and water reabsorption. It presents as oliguric prerenal AKI with edema and low urinary sodium. Septic shock and other causes of AKI must be ruled out. TA-TM is defined by hemolytic anemia with erythrocyte fragmentation, thrombocytopenia, and renal failure. It is characterized by endothelial damage, leading to thickened glomerular and arteriolar vessels, the presence of fragmented red blood cells, thrombosis, and endothelial cell swelling. In the setting of HSCT, the incidence of TMA ranges from 2% to 21%. The clinical course of TMA can be rapid with severe AKI but commonly follows a more indolent course, resulting in CKD and, possibly, progression to ESRD. Risk factors for the development of TMA after HSCT include CNI use, TBI, and GVHD. The mainstay of TA-TMA management remains CNI dose reductions, or treatment interruptions remain the mainstay of TA-TMA management. Because GVHD can be a risk factor for the development of TA-TMA, an approach with close monitoring of levels, rather than complete cessation, of CNI may be more appropriate. In patients not responsive to these interventions, pharmacologic therapies include rituximab, defibrotide, and eculizumab. Eculizumab, a monoclonal immunoglobulin that binds complement factor-5, has been used for treatment of TA-TMA.

Acute Kidney Injury and Viral Infections in the Setting of Hematopoietic Stem Cell Transplantation

Viral infections are an emergent cause of AKI in bone marrow transplant recipients. Several studies confirm an association between AKI and adenovirus, polyomavirus (BK virus or JC virus), and simian polyomavirus. The well-documented association between the BK virus and hemorrhagic cystitis may explain not only the high incidence of hemorrhagic cystitis after bone marrow transplantation (20% to 25%) but also the occurrence of nephropathy. The simian 40 virus was found to exhibit an association with AKI and hemorrhagic cystitis. Finally, adenovirus is associated with disseminated

infections, encephalitis, pneumonitis, and AKI. To allow either a prompt reduction in immunosuppression or the initiation of antiviral therapy, the diagnosis of adenoviral disease must be made early. Polymerase chain reaction testing or enzyme-linked immunosorbent assay may help to achieve this goal.

Managing Acute Kidney Injury in the Setting of Hematopoietic Stem Cell Transplantation

The management of AKI is mainly supportive and specific to the underlying cause. For situations of renal hypoperfusion, prompt administration of IV fluids is required to restore effective circulating volume. However, a critical point is that fluid overload can be an independent predictor of mortality in critically ill patients. Stem cell transplant recipients are a population that may be particularly sensitive to fluid overload. Judicious use and dose adjustment of antimicrobials should be used to decrease risk of AKI from nephrotoxin exposure. For those not responsive to medical interventions, dialysis is used as supportive therapy for management of AKI-related fluid and metabolic derangements. The most recent literature cites a risk of dialysis ranging from 0 to 30%, higher in patients treated with myeloablative, as compared to those receiving reduced intensity, regimens[20]; in these patients, an extremely high mortality rate, often approaching 80% to 100%, has been reported. In term of dialysis modality, continuous therapies may be more desirable in the intensive care setting, allowing for fluid removal in hemodynamically unstable patients. Furthermore, continuous hemofiltration offers a convective removal of larger inflammatory molecules that cannot be cleared using the diffusive properties of continuous dialysis, and this should improve survival.

HEPATIC SINUSOIDAL OBSTRUCTION SYNDROME

Hepatic SOS, also known as venoocclusive disease (VOD), consists of tender hepatomegaly, fluid retention, weight gain, and jaundice that usually occurs after the administration of high-dose chemotherapy (with or without TBI) as a conditioning regimen in the HSCT setting.[19] The pathophysiology of SOS involves damage to hepatic sinusoidal endothelial cells, which leads to sinusoidal thrombosis/obstruction and portal hypertension. A recent review found that the overall mean incidence of SOS was 13.7%. SOS occurs more commonly after myeloablative allogeneic HSCT than after autologous HSCT.[19] Risk factors for developing SOS include older age, preexisting liver disease, and the concomitant use of other nephrotoxic medications. AKI develops in approximately 50% of patients with SOS and is clinically indistinguishable from the HRS.[19] Patients initially are seen with sodium retention, weight gain, peripheral edema, and ascites accompanied by hepatic dysfunction and hyperbilirubinemia. AKI develops 10 to 16 days post-HSCT, with approximately one half of patients requiring dialysis. Renal biopsies performed in patients with SOS have not shown evidence of structural kidney lesions, confirming the notion that AKI is likely hemodynamically mediated. Mortality is 37% in those patients experiencing AKI and as high as 84% in those patients requiring dialysis. More than 70% patients with SOS recover spontaneously with only supportive therapy, which consists of maintaining sodium and water balance, preserving renal blood flow, and treating symptomatic ascites with repeated paracenteses. For patients with severe SOS, there are no highly effective treatments, although the best results have been achieved with defibrotide, which has a 46% complete response rate. Infusion of heparin and/or ursodeoxycholic acid administered immediately before induction therapy also may be moderately successful as preventive measures.

TUMOR LYSIS SYNDROME

Tumor lysis syndrome (TLS) is characterized by a constellation of metabolic abnormalities resulting from either spontaneous or chemotherapy-induced tumor cell death. Tumor cytotoxicity releases intracellular contents, including nucleic acids, proteins, and electrolytes into the systemic circulation leading to development of hyperuricemia, hyperphosphatemia, hypocalcemia, and hyperkalemia. Clinically, this results in multiorgan effects such as AKI, cardiac arrhythmias, and seizures. TLS is the most common oncologic emergency, and without prompt recognition and early therapeutic intervention, morbidity and mortality are high.

The classification system for TLS is based on the Cairo-Bishop classification[21] that defines laboratory tumor lysis syndrome (LTLS) and clinical tumor lysis syndrome (CTLS) (Table 41.5).

This definition of CTLS assumes that the clinical manifestations are not caused directly by the therapeutic agent. Last, Cairo and Bishop also proposed a system that combines the definitions of no TLS, LTLS, and CTLS, thus grading clinical manifestations in each affected organ to classify the grade of TLS (Table 41.6). Although this grading system attempts to provide uniform definitions to TLS severity, it is not used widely in clinical practice. The Cairo-Bishop classification is not immune to criticism in particular from a renal standpoint; indeed, Wilson and Berns have highlighted that defining AKI on the basis of a creatinine value at least 1.5 times the upper limit of normal does not clearly distinguish CKD from AKI. Thus they proposed to use established definitions of AKI in CTLS such as an absolute 0.3 mg/dL increase or relative 50% increase in creatinine over baseline. Finally, in the Cairo-Bishop classifications the chemotherapy is a required criterion for LTLS and CTLS, meaning that this cannot be applied to spontaneous TLS, which is common with high-risk malignancies.

TABLE 41.5

Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome and Clinical Tumor Lysis Syndrome

Laboratory Tumor Lysis Syndrome (LTLS)	
Metabolites or Electrolytes	
Uric acid	≥8 mg/dL or 25% increase from baseline
Potassium	≥6 mEq/L or 25% increase from baseline
Phosphorus	≥4.5 mg/dL or 25% increase from baseline
Calcium	25% decrease from baseline
Clinical Tumor Lysis Syndrome	
LTLS and one or more of the following:	
• AKI (creatinine ≥ 1.5 ULN)	
• Cardiac arrhythmia or sudden death	
• Seizure	

AKI, Acute Kidney Injury; *ULN,* upper limit of normal.

TABLE 41.6

Grading of Clinical Tumor Lysis Syndrome

	Stage I	Stage Ii	Stage Iii	Stage IV
Renal failure	Serum creatinine = 1.5 UNL or creatinine clearance 30–45 mL/min	Serum creatinine = 1.5–3 UNL or creatinine clearance 20–30 mL/min	Serum creatinine = 3–6 UNL or creatinine clearance 10–20 mL/min	Serum creatinine > 6 UNL or creatinine clearance < 10 mL/min
Cardiac arrhythmia	Intervention not indicated	Nonurgent intervention indicated	Symptomatic and incompletely controlled or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with cardiac heart failure, hypotension, syncope, shock)
Seizures	None	One brief generalized seizure; seizure(s) well controlled by anti-convulsivant, or infrequent focal motor seizures	Seizure in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizure of any kind which is prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)

TLS is described most commonly in NHL, as well as other hematologic malignancies, such as acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML), and less commonly in chronic leukemias and MM. More rarely, TLS also has been described in patients with solid malignancies having particular features, such as large tumor burden, metastatic disease (especially) in the liver, short doubling time, increased chemosensitivity, and elevated baseline uric acid and LDH.[22] Among solid tumors, small-cell carcinoma of the lung (SCLC) and germ cell tumors are those most frequently associated with the development of TLS. TLS usually is associated with cytotoxic chemotherapy, but reports also have linked it to the use of targeted therapies such as imatinib, bortezomib, rituximab, and with corticosteroids, methotrexate, and thalidomide. Last, TLS also may be spontaneous, that is, not requiring initiation of cytotoxic therapy, as a result of rapid cell turnover and an increased rate of purine metabolism.

The incidence of TLS varies based according to the underlying malignancy and to the definition of TLS. Most incidence data are from old, retrospective studies that preceded the Cairo-Bishop classification, leading to a considerable heterogeneity in the resulting figures, which range from 18.9% to 56 % for LTLS and from 5% to 11% for CTLS.

Risk Factors for Tumor Lysis Syndrome

Risk factors for TLS include cancer-specific and patient-specific factors.[23] Increased tumor burden is the most cancer-specific risk factor; elevated LDH, white blood cell count > 50,000/mm^3, massive liver metastasis, bone marrow involvement, cancer stage, proliferation rate of cancer cells, and cell sensitivity to cytotoxic therapy also can play a key role. Patient-related factors include age, volume depletion, preexisting CKD, hyperuricemia, and hyponatremia. Recognition of these high-risk factors is an important step in the management of TLS.

In 2008 an expert panel[22] developed a TLS risk classification system, based on published evidence and expert opinion, in which malignancies were described as having a low (<1% chance), intermediate (1%–5% chance), or high (>5% chance) risk for developing TLS. Classification into these risk groups incorporates type of histology, extent of disease, renal involvement or dysfunction, and type of induction therapy.[23]

Pathophysiology of Tumor Lysis Syndrome

TLS is a direct consequence of cell lysis and release of intracellular products. When clearance of these products is impaired and their serum burden increases, the clinical sequelae of TLS may occur. Of these cellular products, nucleic acids (converted to uric acid), potassium, and phosphorus are particularly important in the pathophysiology of TLS. The nucleic acids adenine and guanine are metabolized to xanthine, which is metabolized further by xanthine oxidase to the water-insoluble uric acid (Fig. 41.2).

Uric acid is freely filtered at the glomerulus, and handling in the renal proximal tubule is a combination of reabsorption and secretion mediated by luminal urate/anion exchanger urate transporter 1 (URAT-1) and the basolateral organic anion transporter (OAT). When the capacity to transport luminal uric acid is overwhelmed, there is potential for uric acid to crystallize within the tubular lumen. An acidic urine pH favors this process. Uric acid crystals can cause direct tubular injury by obstruction. Furthermore, intratubular and parenchymatous uric acid precipitations causes renal injury by a granulomatous reaction and necrosis of the distal tubule epithelium through induction of chemokine-mediated inflammation from monocyte chemoattractant protein-1 (MCP-1) and macrophage migration inhibition factor (MIF). There are also crystal-independent mechanisms, which target hemodynamics: these include increased peritubular capillary pressures, increased vasoconstriction, and decreased blood flow. Uric acid also may prevent recovery from AKI in TLS, because it has been shown to inhibit proximal tubule cell proliferation. These diverse mechanisms are united in their propensity to cause AKI, as reported in Fig. 41.3.

Massive tumor cell lysis releases potassium into the extracellular environment, leading to severe hyperkalemia, especially in the setting of CKD or AKI.

Because phosphate is an intracellular electrolyte, cell lysis releases significant amounts of it. However, malignant hematologic cells may contain four times more intracellular phosphate in comparison to normal mature lymphoid cells, making hyperphosphatemia a particular issue with tumor cell lysis; hyperphosphatemia occurs when the kidney's excretory capacity is overwhelmed. Thus preexisting CKD or AKI enhances the risk of hyperphosphatemia within TLS. Hyperphosphatemia exerts its predominant toxicity by binding to calcium cations, and consequentially calcium-phosphate precipitates may deposit in tissues, including the renal interstitium.

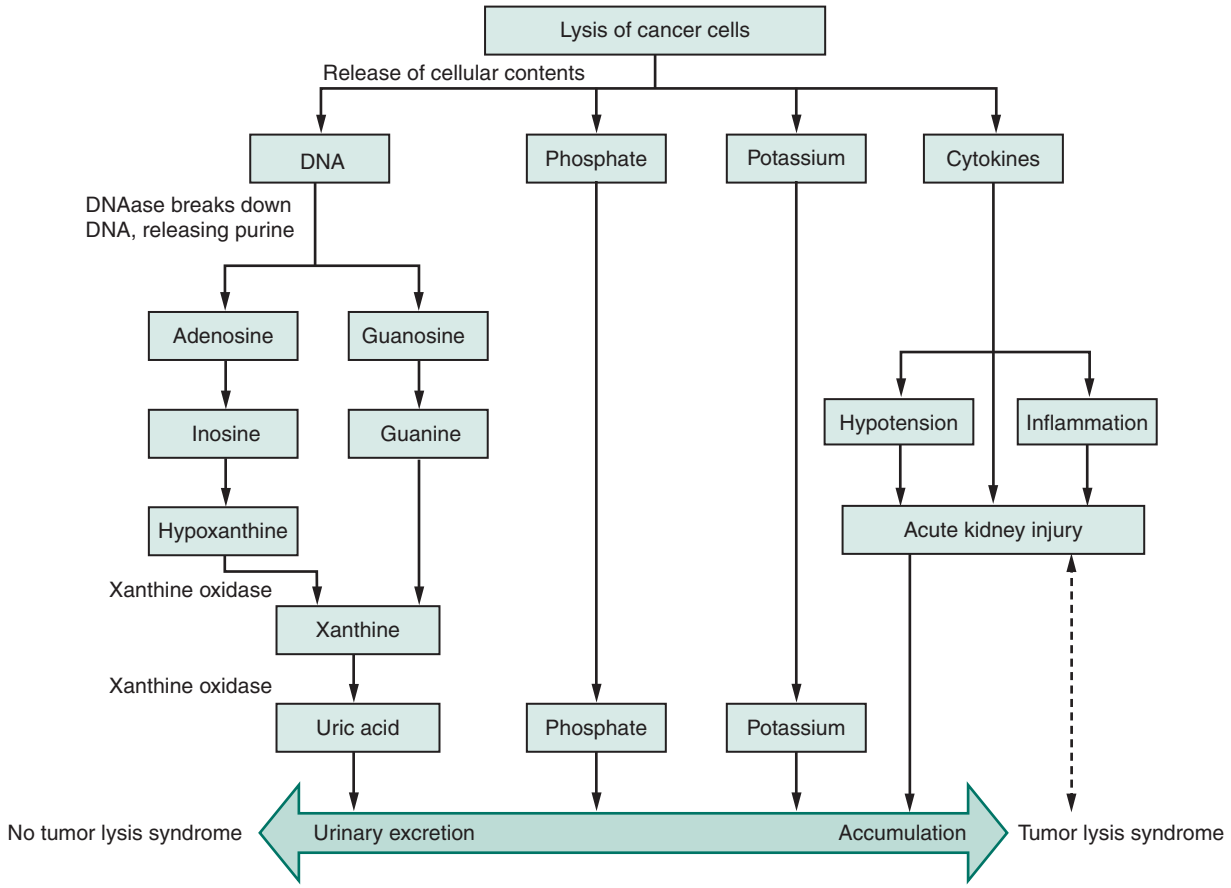

FIGURE 41.2 Proposed pathophysiology of tumor lysis syndrome.

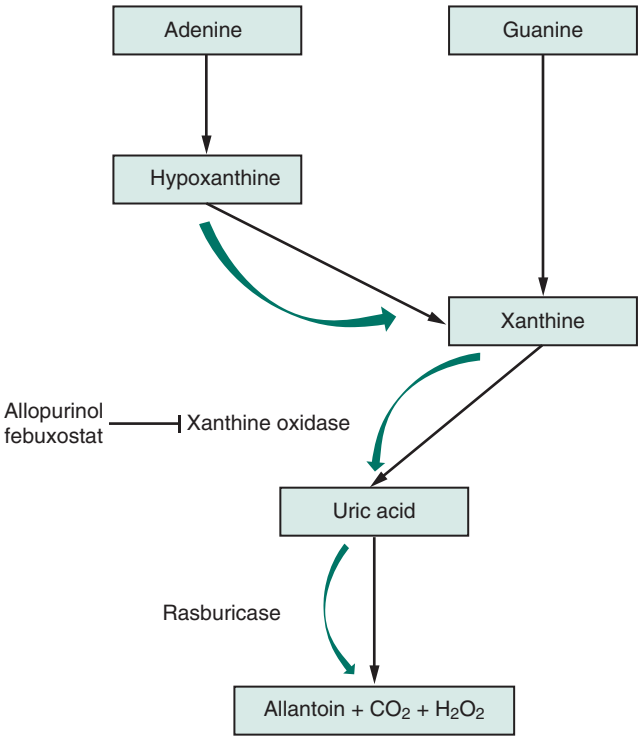

FIGURE 41.3 Principles of therapy for the prevention or treatment of tumor lysis syndrome.

TABLE 41.7

Mechanisms of Nephrotoxicity From Uric Acid

Tubular Obstruction	Tissue Damage	Acute Inflammation
Uric acid crystals	Endothelial dysfunction (nitric oxide mediated)	Correlates with circulating cytokines
Mechanical obstruction	Platelet activation	Stimulates synthesis of MCP-1
Tubular nephropathy	Oxidant stress and cell disruption	Stimulate monocyte production of interleukin-1β and tumor necrosis factor-alpha

MCP-1, Monocyte Chemoattractant Protein-1.

AKI in TLS may be due to the mentioned effects of acute urate nephropathy or hyperphosphatemic nephrocalcinosis affecting the renal tubulointerstitium or a combination of the two (Table 41.7). The association between AKI and TLS has been demonstrated across various populations and tumor subtypes ranging from 20% to 45% in hematologic cancer patients.

Prevention and Treatment of Tumor Lysis Syndrome

Prevention of TLS begins with recognition of risk factors and close laboratory and clinical monitoring. Patients at highest

risk of developing TLS require intensified monitoring with more frequent electrolyte checks.[22] Patients with high-risk disease may be prone to lactic acidosis from massive tumor cell necrosis. Because acidosis inhibits uric acid excretion, prompt recognition and correct of acidosis may prevent or ameliorate uric acid nephropathy. In addition, nonsteroidal antiinflammatory drugs, iodinated radiocontrast dye, and other potentially nephrotoxic therapeutic agents should be avoided to abrogate the risk of AKI from TLS.

Volume Expansion

Volume expansion supports adequate intravascular volume and renal blood flow, which maintain glomerular filtration. This is the cornerstone of uric acid, potassium, and phosphate excretion and may delay and prevent the need for renal replacement measures.[22] High-dose IV saline up to 3 L has been recommended. Diuretics may be necessary if patients develop volume overload, but routine use is not recommended to avoid volume depletion.

The formerly widespread use of urinary alkalinization is now a controversial practice. Alkalinization makes physiologic sense because increasing urine pH from 5 to 7 can increase the solubility of uric acid more than 10-fold; however, urinary alkalinization decreases calcium-phosphate solubility, thereby exacerbating its precipitation and deposition. Furthermore, if urinary alkalinization results in rising serum pH, free calcium may bind albumin more avidly and further exacerbate hypocalcemia. Thus urinary alkalinization is not recommended in the management of TLS.

Allopurinol

Allopurinol is converted in vivo to oxypurinol and as a xanthine analogue acts as a competitive inhibitor of xanthine oxidase and blocks the conversion of purines to uric acid (see Fig. 41.2). This prevents hyperuricemia but does not treat preexisting hyperuricemia. Administration of allopurinol is recommended for prophylaxis in patients with low and intermediate risk of developing TLS.[22] Because oxypurinol excretion is by the kidney, dose adjustments are necessary for patients with CKD and AKI. Allopurinol reduces the clearance of purine-based chemotherapeutic agents such as 6-mercaptopurine and azathioprine. It also may interact with azathioprine and cyclophosphamide in potentiating severe bone marrow suppression, so these association must be avoided.

Febuxostat

Febuxostat is a novel xanthine oxidase inhibitor lacking the hypersensitivity profile of allopurinol. Because it is metabolized to inactive metabolites by the liver, adjustment for reduced eGFR is not necessary. It has been proposed as a viable alternative to allopurinol in TLS prophylaxis for patients with allopurinol hypersensitivity or renal dysfunction.[22]

Rasburicase

Rasburicase is an *Aspergillus*-derived recombinant urate oxidase approved for the management of hyperuricemia in patients with leukemia, lymphoma, and solid tumor malignancies receiving anticancer therapy. Rasburicase catalyzes the conversion of uric acid to allantoin, carbon dioxide, and hydrogen peroxide (see Fig. 41.2). Indeed, allantoin is 5- to 10-fold more soluble than uric acid and is excreted readily.

There are no prospective studies that have examined the impact of rasburicase on relevant clinical end points such as morbidity from AKI. Nonetheless, rasburicase should be used for prophylaxis in patients with high risk of developing TLS.[22] The FDA-approved dosing guidelines recommend 0.2 mg/kg in 50 mL normal saline as a 30-minute IV infusion once daily for up to 5 days. Length of treatment is related to control of plasma uric acid levels, but use of rasburicase for more than 5 days is rarely needed; and in most published studies, one-time dosing was sufficient to suppress hyperuricemia.

Rasburicase does not require dosing adjustment for eGFR and is not known to have any known clinically relevant drug-drug interactions. Rasburicase is active ex vivo, so blood samples for serum uric acid levels must be stored on ice to avoid erroneously low results. Patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency can develop significant methemoglobinemia and hemolysis as a result of oxidative stress triggered by hydrogen peroxide.[22] Accordingly, patients should have G6PD status tested before starting rasburicase.

Renal Replacement Therapy

The need for RRT has reduced significantly since the advent of rasburicase, but about 1.5% of children and 5% of adults require dialysis during induction therapies. Indications for RRT are similar to those for AKI from other causes, but because of the rapid onset of the clinical manifestations of TLS, the threshold for initiating dialytic therapies is lower than in other situations. Although intermittent hemodialysis may be sufficient for most patients, continuous RRT at high dialysate or replacement fluid flow rates (>3–4 L/h) may be necessary in those patients with severe TLS who experience rebound in serum potassium and phosphorous levels with intermittent hemodialysis.

THROMBOTIC MICROANGIOPATHIES

TMAs are a spectrum of disorders between the two classical entities of thrombotic thrombocytopenic purpura (TTP) and HUS; TMA may be associated with the cancer, with cancer chemotherapy, or with HSCT.[24]

Thrombocytopenia with microangiopathic hemolytic anemia and no alternative diagnosis is considered sufficient to establish a presumptive diagnosis of TMA. Currently, the incidence of cancer drug–induced TMA during the last few decades exceeds 15%, primarily because of the introduction of anti-VEGF agents.

In general, TMA in cancer patients can be classified as:

1. Cancer-related TMA
2. Cancer drugs–induced TMA (Table 41.8)
   - Type I cancer drugs–induced TMA is caused by chemotherapy regimens that can potentially promote long-term kidney injury, as well as increased morbidity and mortality
   - Type II cancer drugs–induced TMA is caused mainly by anti-VEGF agents that are not typically associated with cumulative dose-dependent cell damage
3. HSCT-related TMA[25]

TABLE 41.8

Characteristics of Type I and Type II Drug-Induced TMA

	Type I	Type Ii
Causative agents	Mitomycin-C, gemcitabine, platinum salts, combination regimens of cytotoxic chemotherapeutics	Targeted therapies
Timing of onset	Usually 6–12 months after starting therapy	Occurs any time after the initiation of treatment and may be observed after prolonged treatments
Dose relationship	Yes	No
Localization of pathologic alterations	Arteriolar and glomerular capillary thrombosis	Exclusive glomerular capillary thrombosis
Clinical manifestations	• Hematologic manifestation usually present • Hypertension • Acute kidney injury • Pulmonary edema • ARDS	• Hematologic manifestations only in half patients • Hypertension • Varying degrees of proteinuria without kidney failure
• Outcome	• Irreversible damage • Increased morbidity and mortality • High incidence of acute mortality (4-month mortality up to 75%) and chronic kidney disease requiring dialysis despite drug discontinuation, steroids, or plasma exchange	• High likelihood of recovery after interruption (reversible) • Reportedly does not affect mortality • Patients' and kidney survival rates are excellent after stopping causative agent(s)

Cancer-Related Thrombotic Microangiopathies

Most of the cases occur in patients with solid tumors, the most common type being adenocarcinomas (of the stomach, breast, and lung); however, TMA also has been reported in patients with other solid tumors or hematologic malignancies.[26] The pathophysiology of the TMA-malignancy association remains controversial. Several potential pathophysiologic mechanisms have been proposed over time. Because cancer-related TMA occurs primarily in patients with mucin-producing adenocarcinomas, it has been speculated that mucin may exert a direct deleterious effect on the injured endothelium, affecting the production and release of von Willebrand factor. TMA also may be caused or aggravated by direct contact between erythrocytes and circulating carcinoma cells, as well as by tumor emboli within small blood vessels, which have been observed at autopsy. Cancer-related TMA also may develop because of injury to the vascular endothelium associated with a decreased ADAMTS13 activity, without the presence of anti-ADMTS13 antibody.

Cancer Drugs–Induced Thrombotic Microangiopathies

It is more common than cancer-related TMA. In the past, a clinically suspected drugs-induced TMA has been estimated to account for 15% of TMA cases overall. Currently, TMA incidence has increased and antitumor therapy has become its commonest cause in cancer patients. A cancer drugs–induced TMA diagnosis should be considered in the presence of cytopenia. In this circumstance, anemia and thrombocytopenia can be linked to myelotoxicity secondary to chemotherapy or to drug-induced TMA. Helpful clues to recognize drug-induced TMA include (1) the timing of drug initiation and the subsequent clinical syndrome (onset of worsening hypertension and proteinuria), (2) partial or complete recovery after drug withdrawal, and (3) precedent reports of a similar drug class being associated with TMA.[25]

Furthermore, because kidney involvement is predominant in cancer drugs–induced TMA, kidney biopsy could be performed to confirm the diagnosis.

Type I Cancer Drugs–Induced Thrombotic Microangiopathies

Clinical and pathologic symptoms of drug-induced TMA result from a dose-dependent toxicity. The clinical course of TMA can be variable, with worsening kidney function not becoming evident until months after initiation or discontinuation of drug therapy.[25] Usually, patients have been treated with multiple drug courses and are experiencing clinical remission when they develop a microangiopathic hemolytic anemia and thrombocytopenia. In addition, the classic laboratory features of TMA are not always present. New-onset or worsening hypertension is often an early clue to the diagnosis. Neurologic dysfunction is not a consistent feature of chemotherapy-related TMA because there are usually limited extrarenal manifestations. There is continued speculation about the pathogenesis of chemotherapy-related TMA. Microvascular thrombosis is the key event, but it is not clear whether this results from direct endothelial toxicity or from immune-mediated effects on ADAMTS13 levels or other potentially damaging activity.[6,20] Different chemotherapeutic agents have been associated with TMA, including mitomycin C, gemcitabine, platinum salts (administered either as monotherapy of within combination regimens), pegylated liposomal doxorubicin, and high-dose cyclophosphamide, especially when combined with radiation therapy within programs of HSCT. Notably, anthracyclines have been associated with TMA only when administered in combination with mitomycin-C and 5-fluorouracil.

Type II Cancer Drugs–Induced Thrombotic Microangiopathies

Almost all anticancer targeted agents, especially inhibitors of the VEGF/VEGFRs pathway, have been linked with the development of a syndrome characterized by new-onset hypertension (or exacerbation of preexisting hypertension), kidney injury (AKI or chronic kidney disease), with or without proteinuria, and histopathologic features of kidney TMA.[25] Half of the TMA cases were limited to the kidney without microangiopathic hemolytic anemia

or thrombocytopenia. Pathologic TMA features limited to the glomerular structures differentiate anti–VEGF-induced TMA from other causes of TMA, including those secondary to gemcitabine or other chemotherapeutics. Kidney function usually can be preserved combining antihypertensive agents with the withdraw of the anti–VEGF/VEGFRs agent. Hypertension and proteinuria resolved after drug discontinuation and use of antihypertensive agents. In one case report, successful recovery of sunitinib-related TMA after plasmapheresis was reported.

Management of Thrombotic Microangiopathies in Cancer Patients

Effective management of TMA first requires accurate and rapid diagnosis. Historically, the prognosis of chemotherapy-induced TMA was catastrophic, with a mortality rate reported to be more than 50%. The efficacy rates for most TMA therapies were suboptimal, at best: steroids, 36%; plasma exchange, 30%; dipyridamole, 19%; and aspirin, 18%.[6] Second-line therapies included extracorporeal immunoadsorption therapy with staphylococcal protein A columns (45.4% response rate).

Therefore it is obvious that more effective and specific treatment options are needed urgently to improve outcomes. Clear guidelines for treating cancer- or cancer drugs–associated TMA do not exist, and optimal treatment has yet to be proved.

However, two steps may be proposed: general supportive care and specific treatments.

General Supportive Care

Supportive care alone can allow for eventual full recovery in many cases, in particular for those patients who have developed TMA associated with anti-VEGF agent therapy. Supportive care includes the following:

1. Immediate discontinuation of the offending drug and effective blood pressure control with renin angiotensin inhibitors
2. Reintroduction of the drug at lower doses, which may be a useful strategy to avoid recurrent TMA while allowing for continued antitumor treatment. However, it may be difficult to choose an appropriate dose for treatment rechallenge
3. Focus on strict monitoring with early recognition of the signs and symptoms of TMA and careful consideration of the potential risks and benefits for the patient
4. Beyond plasma exchange, fresh frozen plasma infusions and corticosteroids often are used when severe symptoms supervene or clinical improvement is lacking after withdrawal of the offending drug; the utility and timing of these additional measures is not clear.[25] Plasma exchange has been shown to improve prognosis in the general population of patients with TMA, as well as in the case of severe TMA in an ICU setting, although both studies excluded patients with cancer-related TMA. Moreover, plasmatherapy is known to be rarely effective in this setting; indeed, the recent guidelines of the British Society of Haematology did not recommend the use of plasmatherapy in cancer-related TMA or in TMA after HSCT.[27] Effective treatment for this group of patients is thus lacking. Protein-A column immune absorption has been proposed as a possible treatment, without strong evidence of its effectiveness (the grade of recommendation by the British Society of Haematology is, in fact, C)
5. Worsening of kidney function often prompts use of hemodialysis to support the patient in hopes of recovery

Specific Treatments

For patients with atypical HUS refractory to plasma exchange, eculizumab has resulted in clinical remission in selected cases. Likewise, rituximab has shown a high response rate without severe toxicity in a trial of refractory TTP and should be considered for these patients.

Unfortunately, these agents reportedly proved to be useful only within small case series of just single case reports.

Eculizumab, in particular, appears a promising therapeutic option for patients with severe cancer drugs–induced TMA. However, because its cost is prohibitive, the underlying mechanism of eculizumab in all forms of drug-induced TMA must be investigated and the drug's risk/benefit should be studied in prospective trials before its widespread use.

Thrombotic Microangiopathy After Hematopoietic Stem Cell Transplantation

TMA is a common cause of late-onset AKI in patients who have undergone HCT followed by hematopoietic stem cell transplantation. TMA after these complex (and toxic) procedures resemble HUS and usually occur 20 to 99 days posttransplant, more frequently allogeneic (8%–12%) as compared to autologous, transplantation.

The diagnosis of TMA can be challenging, because characteristic features such as anemia, thrombocytopenia, and renal insufficiency are common in patients treated this way, and evidence of schistocytes or elevated serum LDH levels is also not entirely reliable.[25] Hypertension is often present. Urinalysis can be normal or show variable proteinuria and/or hematuria, and cellular casts may be seen on urine sediment. Renal biopsy rarely is needed to establish the diagnosis, except when the presentation is atypical. Typical histology includes mesangiolysis, basement membrane duplication, glomerular endothelial cell swelling, and tubular injury with interstitial fibrosis. The pathogenesis of TMA after HSCT is not well understood, but damage to renal endothelial cells likely plays a key role. It is unclear whether transplantation-associated microangiopathy is a complication of allogeneic HSCT "per se", because TMA often can be attributed to prior chemotherapy, GVDH, high-dose chemotherapy, TBI, SOS, and/or disseminated infections. The management of HSCT-associated TMA is otherwise largely supportive. Calcineurin inhibitors typically are discontinued, although there is no substantial evidence that this discontinuation is necessary, especially in patients who require these medications for life-threatening GVHD. Other oral agents that can be used for the prevention and treatment of GVHD include mycophenolate mofetil and corticosteroids. Substitution of calcineurin inhibitors with daclizumab, a humanized monoclonal antibody against the α-chain of the IL-2 receptor, has been shown to improve TMA in patients with GVHD and TMA. Rituximab, a monoclonal antibody against CD20, and defibrotide also have shown effectiveness in treating HSCT-associated TMA in small, uncontrolled studies. Given its important role in the treatment of non–HSCT-associated TMA, plasmapheresis sometimes is used to treat HSCT-associated TMA, but there is no established proof of benefit with this approach.[25] Patients diagnosed with TMA are at higher risk for transplant-associated complications, including systemic

infections and acute GVHD, and they have greater 180-day mortality. Renal prognosis in these patients is also poor, with the development of TMA increasing the risk of AKI, CKD, and ESRD requiring long-term dialysis.

ACUTE KIDNEY INJURY IN RENAL CELL CARCINOMA AND UROTHELIAL CANCERS

Cancers of renal parenchyma or of urinary tract (from renal pelvis to bladder) often are associated with AKI because of intrinsic and extrinsic causes.

Renal Cell Carcinoma

Renal cell carcinoma (RCC) remains the only malignancy in which either total or partial nephrectomy is indicated in the majority of patients, irrespective of the presence of distant metastases; although the numbers of cytoreductive nephrectomies are decreasing in the era of targeted therapies (as compared with the era of cytokines), available data suggest that the benefit of removing the kidney even in the presence of distant metastases is huge also in the present era of targeted agents.

However, it has been clearly demonstrated that patients who have undergone radical nephrectomy are at increased risk of developing AKI, especially in the presence of certain comorbidities, or of an acute worsening a preexistent CKD, which is highly prevalent in these patients before surgery. As far as partial nephrectomy, which usually is considered to be nephron sparing, we should acknowledge that it also may cause AKI, depending on the amount of nonneoplastic parenchyma removed, as well as of the underlying conditions of the renal parenchyma (not to take into account possible, although fortunately rare, surgical complications).

Notably, the knowledge of those risk factors that may cause AKI (as well as CKD) after these procedures should be discussed with the operating urologist before nephrectomy.

Nephrectomized patients who develop AKI are at a higher risk of developing CKD, which may worsen patients' prognosis, hamper the administration of active oncologic treatment, or exacerbate its toxicities.

Urothelial Cancers

Cancer can damage the kidneys directly in a variety of ways. Renal compression or urinary tract obstruction by a tumor close to the kidney, such as ovarian or bladder tumor, frequently is seen in patients with cancer. Metastatic solid tumors usually result in AKI through involvement of the lymph nodes, causing ureteric obstruction and vascular occlusion. In urothelial tumors, AKI is caused either by obstruction because of the presence of cancer either by its treatments: surgery, stenting, or chemotherapy (Table 41.9).

TABLE 41.9

Risk Factors for Acute Kidney Injury in Urothelial Cancers

Therapeutic Procedure	Mechanism(S) Leading to Acute Kidney Injury
Urinary stenting (percutaneous or internal)	Relapsing infections Obstructions
Neoadjuvant and/or adjuvant chemotherapy	• Cisplatin-induced nephrotoxicity • From the Surveillance, Epidemiology and End Results (SEER) database we know that just a minority of urothelial cancer patients are able to receive CDDP-based chemotherapy, in the vast majority of cases because of coexisting CKD
Surgery Nephrectomy Cystectomy	• Reduction in nephron mass • Chronic relapsing infections • Hydronephrosis • Acute obstructions

ACUTE KIDNEY INJURY IN ABDOMINAL COMPARTMENT SYNDROME

Abdominal compartment syndrome (ACS) is defined most commonly as an intraabdominal pressure (IAP) >10 and clearly >20 mmHg with evidence of organ dysfunction that improves with abdominal decompression. Patients may present with tachypnea with high ventilator pressures, liver dysfunction, intestinal ischemia, and oliguric AKI. In patients with cancer, common causes include malignant ascites, urinary leak from a recent urologic procedure, and colonic dilatation. The IAP, which is measured by transducing a Foley catheter filled with saline with a pressure monitoring system, is normally 0 to 10 mm Hg. Values between 12 and 20 mm Hg are classified as intraabdominal hypertension and generally are not associated with organ dysfunction. Depending on the cause, treatment may involve diuretics, paracentesis, colonic decompression with nasogastric suction, and decompression laparotomy. Generally, urine output and renal function markedly improve with therapy.

CONTRAST-INDUCED NEPHROPATHY IN CANCER PATIENTS

Intravascular administration of iodinated contrast is associated with contrast-induced nephropathy (CIN). Risk factors include underlying CKD, diabetes mellitus, volume depletion, and coadministration of other nephrotoxins. Intraarterial injection is considered to be more nephrotoxic compared with IV administration. In addition, high osmolar (>1400 mOsm/kg) and low osmolar (600–800 mOsm/kg) contrast agents are associated with a higher incidence of AKI in comparison to isoosmolar (300 mOsm/kg) contrast, that is, the most widely used in clinical practice. Preventive measures should be used in patients with an eGFR less than 60 mL/min, including limiting contrast volume, using isoosmolar contrast, prehydration with normal saline, and discontinuation of concurrent nephrotoxic agents. Several meta-analyses have examined the use of N-acetylcysteine in the prevention of CIN[28], but results remain inconclusive, as in the case of bicarbonate administration. There is insufficient evidence to recommend hemodialysis or hemofiltration for the prevention or treatment of CIN.

Notably, because in cancer patients AKI is usually multifactorial, the administration of contrast medium is often just one of many different concomitant causes contributing

to the onset of AKI; indeed, the use of nephrotoxic agents such as CDDP or bisphosphonates in close proximity to the administration of contrast medium may greatly increase the likelihood of an acute CIN. Thus an important issue is how to deal with these potentially nephrotoxic agents when a contrast-enhanced radiologic procedure (usually a CT scan) is scheduled, in particular, if and when such therapies should be stopped before the administration of contrast medium.

CONCLUSION

AKI is a serious complication of cancer or of its treatments and is responsible for additional morbidity and mortality. The renal dysfunction results from various causes, including metabolic disturbances, renal infiltration by malignant cells, sepsis, and drug-induced toxicity. Prevention of AKI is mandatory in patients with cancer to improve oncologic outcome and to ameliorate oncologic treatment, thereby preventing unnecessary dose reduction or suspension. Protecting against AKI involves the identification of those patients most at risk and, when applicable, preventive strategies (when feasible) and timely and adequate therapeutic interventions. AKI from highly predictable causes (e.g., contrast agent–induced nephropathy and TLS) absolutely should be avoided. Fluid expansion and uricolytic treatment in patients with a high risk of acute TLS, prevention of contrast agent–induced nephropathy, scrupulous avoidance of nephrotoxic drugs in high-risk patients, and monitoring of serum methotrexate concentrations are among the measures that may reduce the risk of AKI in these patients. Advances in supportive care including RRT have improved outcomes in critically ill patients with cancer, with the exception of patients undergoing allogeneic stem cell transplantation. A joint decision-making process between oncologists, ICU specialists, and nephrologists is vital to determine which patients are best suited for RRT. Identification of risk factors for AKI, as well as the development of biomarkers of kidney injury, may lead to earlier intervention. Further studies are needed to improve the prognosis for these patients, to determine optimal treatments, and to identify additional causative factors. A multidisciplinary approach[29] that incorporates adequate assessment, use of appropriate preventive measures, and early intervention is essential to reduce the incidence of life-threatening AKI in patients with cancer.

Key Points

1. Kidney disease is a frequent and increasing complication of cancer.
2. There is a bidirectional relationship between cancer and kidney disease.
3. Acute kidney injury in patients with cancer is associated with increased morbidity and mortality.
4. A multidisciplinary approach and early intervention are needed to ensure adequate assessment and to reduce the incidence of life-threatening acute renal failure in patients with cancer.
5. Onconephrology is a growing area of nephrology that requires clinicians to have a better understanding of the renal complications of cancer including acute kidney injury.

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