Chapter 3: AKI Associated With Malignancies

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INTRODUCTION

Advances in treatment, risk stratification, and supportive care have improved survival of patients with cancer over the last two decades (1). AKI may result from the cancer itself (e.g., infiltration or obstruction), the treatment of cancer (e.g., chemotherapy toxicity), or associated complications (e.g., sepsis). Cancer, by itself, is not a contraindication for starting RRT, even in the setting of multiorgan failure (2–4). However, decision-making is complex and requires a multidisciplinary approach between the oncologist, intensivist, and nephrologist. The development of AKI may lead to longer length of hospital stay, decreased functional status and quality of life, and exclusion from further cancer therapy. AKI and RRT may lead to unpredictable levels of chemotherapeutic agents and anti-infective drugs. AKI may also increase inflammatory cytokines in the lung, leading to increased vascular permeability (5) and the need for mechanical ventilation (6). Therefore, early detection and prevention of AKI is crucial in patients with cancer.

DEFINITION

More than 35 different definitions for AKI have been used in the literature, which has made cross-comparisons between studies difficult. This led to the development of the RIFLE classification, which defined three stages of AKI (risk, injury, and failure) and two stages of renal failure requiring dialysis (loss and ESRD) (7). Stages for AKI are determined by the percent rise in serum creatinine relative to baseline, decreased urine output, or the need for dialysis. It is unclear whether the criteria are well balanced in respect to urine output and serum creatinine, as most studies have not utilized the urine output component. The RIFLE classification has been validated in numerous patient populations and has highlighted the significant effect of mild degrees of renal injury on mortality. Significant renal injury may occur without elevation in serum creatinine, and an elevation of 0.3 mg/dL has been associated with increased mortality in hospitalized patients.

The Acute Kidney Injury Network (AKIN) proposed modifications to the RIFLE criteria with three stages of AKI corresponding to the risk, injury, and failure categories (8). Patients with an absolute rise in serum creatinine of 0.3 mg/dL are included into the least severe category (stage 1). The loss and ESRD categories were eliminated, and all patients requiring dialysis were classified into the most severe category (stage 3). Last, a time constraint of 48 hours to reach stage 1 was also included in the AKIN definition. Whether the AKIN modifications to the RIFLE criteria have led to improvements in classification has yet to be determined (9). Recently, The Kidney Disease Improving Global Outcomes (KDIGO) work group combined elements of the RIFLE and AKIN classifications to define AKI as 1) an increase in serum creatinine (SCr) $\geq$0.3 mg/dL within 48 hours, 2) an increase in SCr to $\geq$1.5 times baseline within the prior 7 days, or 3) a urine volume of $<$0.5 mL/kg/h for 6 hours. Severity of AKI is staged similar to the AKIN criteria. Several studies have correlated AKI as defined by these criteria with increased mortality, length of stay, and hospital costs in patients with cancer (10–13).

EPIDEMIOLOGY AND PROGNOSIS

AKI is common in hospitalized patients with cancer and is associated with increased length of stay and hospital costs. In a Danish population-based study of 1.2 million cancer patients, the incidence of AKI defined by the RIFLE criteria was highest in patients

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with renal cell cancer (44%), multiple myeloma (33%), liver cancer (32%), and leukemia (28%) (14). Compared with patients without cancer, critically ill patients with cancer have a higher incidence of AKI requiring RRT. Depending on the definition of AKI and the underlying case mix, it has been reported that 13%–42% of critically ill patients with cancer develop AKI and 8%–60% require RRT (15). The incidence is highest for those patients with hematologic malignancies, multiple myeloma, and septic shock.

The 28-day mortality of patients with cancer who require RRT is 66%–88% (16). In one study of critically ill patients with cancer, the odds ratio for 30-day mortality was increased twofold in patients with AKI. However, approximately one-half of the patients with AKI survived to day 30 after admission (17). In one study of AKI in critically ill patients, there was complete recovery of renal function in 82% and partial recovery in 12%, and chronic dialysis was needed in only 6% of patients (18). Overall severity of illness, age, and functional status may have more of an impact on prognosis than underlying malignancy, and the presence of cancer may not be an absolute exclusion criterion for withholding RRT. However, the prognosis of critically ill recipients of stem cell transplants who develop AKI remains poor, with mortality exceeding 80%. A team-based approach between the oncologist, critical care physician, and nephrologist is necessary to identify patients who are most suitable for initiation of RRT.

ASSESSMENT OF KIDNEY FUNCTION

The ideal marker of kidney function would be a substance that is freely filtered, neither secreted nor reabsorbed, and is solely eliminated by the kidney. Although inulin and radiolabeled EDTA and iothalomate demonstrate many of these characteristics, their complexity and cost of measurement have precluded use in daily practice. Serum creatinine has been traditionally used as a marker of kidney function, but when used in isolation, it is not an adequate measure. Serum creatinine values are altered by many other factors including muscle mass, diet, sex, and tubular secretion. Patients with cancer may present with spuriously low serum creatinine levels secondary to cachexia. However, estimating equations for GFR, which factor other variables such as age, sex, and race along with serum creatinine, provide a reasonable estimate of renal function in most patients. The most commonly used estimating equations are the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD), and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas. Among patients with cancer who have serum creatinine values within the normal range, 20% of patients have unsuspected CKD when the GFR is estimated by Cockcroft-Gault formula (19).

It is well understood that elevation in serum creatinine is a relatively late marker of renal injury, as a significant amount of kidney function may be lost before a rise in serum creatinine is apparent. Several urinary biomarkers of AKI that have greater sensitivity for acute renal injury have been proposed, including kidney injury molecule 1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), *N*-acetyl-β-D-glucosaminidase (NAG), interleukin 18 (IL-18), and matrix metalloproteinase 9 (MMP-9). The accuracy and reliability of these markers varies across individual studies. An assay for serum and urinary NGAL levels has become recently available but is not routinely used in the clinical setting at this time.

EPIDEMIOLOGY OF AKI IN CANCER PATIENTS

The overall incidence of AKI among cancer patients was recently defined in a large Danish study. Among 1.2 million people followed between 1999 and 2006, there were 37,267 incident cancer patients with a baseline creatinine measurement. The 1-year risk of AKI in this population (defined as a >50% rise in serum creatinine) was 17.5%, with a 27% risk over 5 years (14). Patients with distant metastases were at the highest risk of AKI. More severe AKI, defined as a doubling of serum creatinine (injury in the RIFLE criteria) (20), 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 (9,613 total), 5.1% required dialysis within 1 year of AKI onset. Older patients were most heavily represented in this analysis.

Cancers with highest AKI risk

Certain cancers carry a much higher risk of AKI than others. In the Danish study above, kidney cancer, multiple myeloma, and liver cancer had the highest 1-year risk of AKI at 44.0%, 33.0%, and 31.8%, respectively. After diagnosis of renal cell carcinoma, many patients still undergo radical nephrectomy, and this procedure itself is associated with a 33.7% risk of AKI and predicts the future development of CKD at 1 year (21).

Patients with acute lymphoma or leukemia undergoing induction chemotherapy are also at an especially high risk of AKI. In a series of 537 patients with either acute myelogenous leukemia or high-risk myelodysplastic syndrome undergoing induction, 36% developed AKI. Even among patients with mild AKI (defined as RIFLE risk), 8-week mortality was 13.6% (95% confidence interval, 7.8%–23%) compared with patients with no AKI whose 8-week mortality was 3.8% (95% confidence interval, 2.2%–6.4%). Patients requiring RRT experienced mortality of 61.7% (95% confidence interval, 50%–74%) over the same time frame (12).

AKI is common in hospitalized cancer patients and also correlates with increased length of stay, cost, and mortality. Candrilli and colleagues analyzed the 2004 Nationwide Inpatient Sample for patients with hematologic malignancies. They identified 350,601 patients without AKI, 27,654 patients with mild or moderate AKI (not requiring dialysis), and 5,148 patients with severe AKI (requiring dialysis). The average length of stay and costs among these groups were 7.4, 12.2, and 17.6 days, and

Table 1. Cancer-specific risk factors for AKI

Age >65 years
Congestive heart failure (i.e., exposure to anthracyclines, trastuzumab)
CKD
Hypovolemia (i.e., chemotherapy-related nausea and vomiting, acute graft-versus-host disease)
Distant metastases
Multiple myeloma
Liver cancer
Nephrectomy for renal cell carcinoma
Induction chemotherapy for acute lymphoma or leukemia

$13,947, $25,638, and $44,619, respectively (22). Cancer-specific risk factors for AKI are summarized in **Table 1**.

ETIOLOGY OF AKI

The causes of AKI in patients with cancer are numerous (**Table 2**). The sites along the nephron at which some of these syndromes act are depicted in **Figure 1**. The specific diagnoses will be discussed in detail elsewhere in the core curriculum, but some notable causes are highlighted in this chapter.

Sepsis

Sepsis is the most common cause of AKI in patients with cancer. In population-based studies, approximately 15% of critically ill patients with sepsis have underlying cancer (23). Acute tubular necrosis secondary to sepsis remains the leading cause of AKI in critically ill patients with cancer. Patients with hematologic malignancies are especially prone to the development of bacterial infections and sepsis secondary to prolonged neutropenia. Nearly half of patients admitted to the intensive care unit (ICU) with hematologic malignancies have underlying sepsis compared with 12%–25% of patients with solid tumors (24). Studies have demonstrated improved survival of cancer patients with sepsis over the last decade, except in patients that require RRT, where hospital mortality approaches 80% (25,26).

Sepsis causes AKI by systemic vasodilation, leading to decreased effective circulating volume, cytokine activation, endothelial damage, and microthrombi formation. The use of vasoconstricting pressor agents further exacerbates an effective prerenal state.

Table 2. Common causes of AKI in patients with cancer

Prerenal azotemia
Volume depletion
Nausea, vomiting, diarrhea
Decreased oral intake owing to mucositis (5-fluorouracil, methotrexate, taxanes)
Polyuria caused by hyperglycemia (steroids) or diabetes insipidus (pituitary tumor)
"Third spacing" (hypoalbuminemia, liver or peritoneal metastases, interleukin-2)
Insensible loss of fluid from skin lesions (mycosis fungoides)
Hemodynamic-mediated
Sepsis
Renal arteriolar vasoconstriction (nonsteroidal anti-inflammatory drugs [NSAIDs], calcineurin inhibitors, hypercalcemia)
Congestive heart failure
Hepatorenal syndrome/hepatic sinusoidal obstruction syndrome
Budd-Chiari syndrome
Intrahepatic inferior vena cava compression or thrombosis caused by hepatomegaly or a tumor
Intravenous iodinated contrast agent
Abdominal compartment syndrome
Intrinsic renal disease
Acute tubular necrosis
Chemotherapy (cisplatin, ifosfamide)
Anti-infectives (amphotericin B, foscarnet, cidofovir, aminoglycosides, vancomycin)
Bisphosphonates
Sepsis
Prolonged prerenal azotemia
Allergic interstitial nephritis (penicillins, cephalosporins, fluoroquinolones, NSAIDs)
Crystal nephropathy (methotrexate, acyclovir, ciprofloxacin, sulfonamides, rifampin)
Osmotic nephrosis (IV immunoglobulin, mannitol, starch)
Thrombotic microangiopathy (post-hematopoietic stem cell transplant, gemcitabine, prior radiation therapy)
Myeloma-related kidney disease
Postrenal obstruction
Bladder outlet obstruction (malignancy of cervix, prostate, bladder, or uterus)
Retroperitoneal disease (metastasis, lymphadenopathy, fibrosis)
Hemorrhagic cystitis (cyclophosphamide, BK virus)
Ureteral strictures (prior radiation therapy, BK virus)

Anti-infectives

The high incidence of sepsis in critically ill cancer patients necessitates the use of nephrotoxic antibacterial and antifungal agents. Aminoglycosides may cause nephrotoxicity after 5–7 days of therapy, and patients present with nonoliguric AKI, hypokalemia, hypomagnesemia, and hypocalcemia. The risk of renal toxicity may be minimized with once daily dosing. Several alternative drugs to aminoglycosides that do not cause AKI have become available in the treatment of neutropenic fever. Amphotericin B deoxycholate may cause tubular toxicity and vasoconstriction, leading to nonoliguric AKI, hypokalemia, hypomagnesemia, and distal renal tubular acidosis. Newer liposomal and lipid formulations are less nephrotoxic with comparable efficacy. Other novel antifungal agents, caspofungin and voriconizole, are also less nephrotoxic and are often used as first-line therapy. Several studies have reported on the nephrotoxicity of vancomycin, although the biological mechanism remains undefined. Reported risk factors for AKI are higher trough levels (>15 mg/dL) and

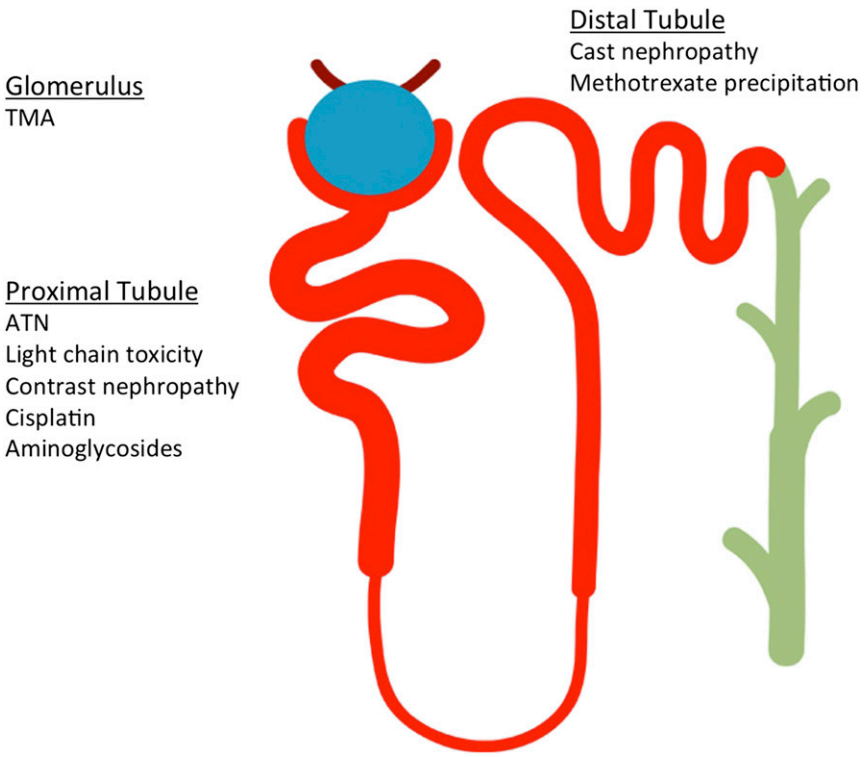

Figure 1. Sites of injury in AKI syndromes. TMA, thrombotic microangiopathy; ATN, acute tubular necrosis.

higher daily doses (>4 g/day) (27,28). Patients present with nonoliguric AKI and bland urine sediment, and most patients recover renal function after discontinuation of the drug.

Chemotherapy

Cisplatin is a DNA alkylating agent used to treat a variety of tumors including sarcomas, small cell lung cancer, ovarian cancer, and germ cell tumors. It is directly tubular toxic and leads to salt wasting, hyponatremia, hypomagnesemia, and AKI. A low chloride environment enhances toxicity, and concurrent saline administration to achieve urine output >3 L/day is the mainstay of prevention. Approximately one-third of patients will experience AKI within days after treatment, and episodes worsen with repeated dosing. Tubular injury may be permanent with doses >100 mg/m^2. Amifostine, a free radical scavenger, has been shown to ameliorate cisplatin nephrotoxicity. Newer platinum agents such as carboplatin and oxaliplatin appear to cause less tubular injury. Ifosfamide is an alkylating agent commonly used in treating sarcomas and metastatic germ cell turmors, which may cause AKI in up to 30% of patients. Proximal tubular injury may also lead to glucosuria, hypokalemia, hypophophatemia, and proximal renal tubular acidosis. Severe cases may present with Fanconi's syndrome. Cumulative doses >100 g/m^2 are associated with moderate to severe tubular injury. Risk factors for AKI include prior cisplatin therapy, tumor infiltration of the kidney, and underlying CKD. Mesna protects against bladder toxicity from metabolites excreted in the urine, which helps prevent hemorrhagic cystitis.

Methotrexate is an antifolate and antimetabolite commonly used in the treatment of leukemia, lymphoma, and sarcoma. High-dose methotrexate (>1 g/m^2) may cause AKI by forming intratubular crystals leading to obstruction and direct tubular cell toxicity. Patients generally present with nonoliguric AKI with a subsequent rapid rise in serum creatinine. Intravenous hydration and urinary alkalinization prevent the precipitation of methotrexate crystals. In the setting of AKI, methotrexate may accumulate and cause neutropenia, hepatitis, mucositis, and neurologic impairment. Folinic acid may be given concurrently to replete folic acid stores and minimize toxicities. Dialysis can acutely clear methotrexate from the blood, but levels quickly rebound after discontinuation of treatment. Carboxypeptidase G2 can rapidly convert methotrexate to an inactive metabolite and recently became commercially available. This therapy also suffers from rebound in plasma levels, but to a lesser degree than high-flux dialysis.

Targeted therapy

Targeted therapy against vascular endothelial growth factor (VEGF) has advanced the treatment of certain tumors including colorectal and renal cell carcinoma. Monoclonal antibody to VEGF (bevacizumab) and tyrosine kinase inhibitors of the VEGF pathway (sunitinib, sorafenib, pazopanib, axitinib, and regorafenib) have been associated with the development of hypertension and

proteinuria (29). Rare cases of thrombotic microangiopathy (TMA) have also been reported (30). Symptoms generally resolve with discontinuation of the drug.

Multiple myeloma

Multiple myeloma involves the clonal proliferation of malignant plasma cells and is the second most common hematologic malignancy after non-Hodgkin lymphoma. Approximately one-half of patients with multiple myeloma present with AKI, and 10% require dialysis on initial presentation (31). The common mechanisms of injury include cast nephropathy, light chain deposition disease, light chain amyloidosis, hypercalcemia, and acute tubular necrosis (ATN) from sepsis. Suppression of normal hematopoiesis predisposes patients to infections and sepsis, which often requires ICU admission. Initial management consists of saline hydration, correction of hypercalcemia, alkalinization of urine, and avoidance of nonsteroidal anti-inflammatory drugs and iodinated contrast. Renal recovery occurs in up to one-half of patients, except in patients who require dialysis, where recovery rates are $<$25%. In a randomized controlled trial, the use of plasma exchange did not significantly decrease the composite end point of death, dialysis dependence, or GFR $<$30 mL/min (32). With concurrent chemotherapy, the use of high cut-off filters with extended daily dialysis may help to decrease circulating monoclonal light chains. Multicenter randomized controlled trials studying the utility of high cut-off hemofilters are currently ongoing.

Hematopoietic cell transplant

The number of hematopoietic cell transplants (HCTs) performed has dramatically increased over the last three decades. Refinement in techniques has permitted transplants in older patients with more comorbidities. All patients, regardless of the type of transplant, are susceptible to infection after transplant until engraftment is complete. During this period, patients are at most risk of developing AKI from ischemic and toxic ATN in the setting of sepsis. Patients who receive allogeneic transplants require calcineurin inhibitors to prevent graft-versus-host disease (GVHD), which further increases the risk of AKI. The need for RRT after HCT increases mortality more than 70% (33,34).

Engraftment syndrome may occur within days after autologous HCT and is a common reason for ICU admission. It is associated with cytokine release in association with rapid neutrophil recovery after HCT. Patients develop fever, noncardiogenic pulmonary edema, erythrodermatous skin rash, and peripheral edema. Often these patients develop nonoliguric AKI with relatively bland urine sediment. The mainstay of treatment is corticosteroids and diuretics, and most patients will recover renal function without the need for RRT.

Hepatic sinusoidal obstruction syndrome (HSOS), formerly termed veno-occlusive disease, is associated with AKI within the first month after allogeneic HCT. Damage to the hepatic sinusoidal endothelium from the pretransplant conditioning regimen leads to sloughing of the endothelium, collagen deposition, fibrosis, and liver failure. In severe cases, patients may subsequently develop AKI from hepatorenal syndrome. Presentation includes right upper quadrant abdominal pain, ascites, edema, and elevated bilirubin. Treatment includes salt restriction, diuretics, and RRT if needed. Severe HSOS, defined as severe liver injury unresponsive to supportive care, often requires ICU admission and is historically associated with near 100% mortality. Defibrotide, an oligonucleotide that has antithrombotic and profibrinolytic properties with minimal anticoagulant effects, has shown promise in patients with severe HSOS. Several clinical trials using defibrotide for treatment of severe HSOS have demonstrated improvement in complete response rates and overall survival, and the drug is currently commercially available in Europe (35,36). A new drug application (NDA) for defibrotide was submitted to the Food and Drug Administration in 2014 and has been granted Fast Track Designation.

TMA occurs in approximately 2%–21% of patients after allogeneic stem cell transplant (37). In one study, 3% of all cancer patients admitted with AKI to the ICU had underlying TMA (4). Patients often present with progressive AKI, anemia out of proportion to underlying renal function, and hypertension. Risk factors for transplant-associated TMA (TA-TMA) are acute GVHD, recipient/donor mismatch, total body irradiation $>$1,200 cGy, and adenovirus infection (37). TA-TMA is not associated with ADAMTS-13 deficiency and is poorly responsive to plasmapheresis. Calcineurin inhibitors are also associated with TMA and should be withheld or decreased in dose if possible.

Contrast-induced nephropathy

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. Intra-arterial injection is considered to be more nephrotoxic compared with intravenous 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 iso-osmolar (300 mOsm/kg) contrast. Preventive measures should be taken in patients with GFR $<$60 mL/min including limiting contrast volume, using iso-osmolar 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 but results remain inconclusive, as is the use of bicarbonate (38). There is insufficient evidence to recommend hemodialysis or hemofiltration for the prevention or treatment of CIN.

Abdominal compartment syndrome

Abdominal compartment syndrome (ACS) is most commonly defined as an intra-abdominal pressure (IAP) $>$10 and clearly

>20 mmHg with evidence of organ dysfunction that improves with abdominal decompression. Patients may present with tachypnea with high ventilatory 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 0–10 mmHg. Values between 12 and 20 mmHg are classified as intra-abdominal hypertension and are not generally associated with organ dysfunction. Depending on the etiology, treatment may involve diuretics, paracentesis, colonic decompression with nasogastric suction, and decompression laparotomy. Generally, urine output and renal function markedly improve with therapy.

CONCLUSION

AKI is a common complication of cancer or its treatment. Advances in supportive care including RRT have improved outcomes in critically ill patients with cancer, with the exception of patients with allogeneic stem cell transplants. A joint decision-making process between the oncologist, intensivist, and nephrologist 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.

TAKE HOME POINTS

- The selection of patients best suited for RRT requires a team-based approach between the oncologist, intensivist, and nephrologist.
- Manifestations of kidney disease from chemotherapy and targeted therapy include AKI, proteinuria, electrolytes derangements, and TMA.
- Nearly one-half of patients with multiple myeloma have evidence of AKI on initial presentation, and 10% require dialysis.
- Engraftment syndrome, HSOS, and TMA are unique causes of AKI in patients after stem cell transplant. The mortality of patients that require dialysis after stem cell transplant remains high.

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REVIEW QUESTIONS

1. Criteria for AKI as defined by the KDIGO classification include the following except:

   a. A rise in SCr ≥0.3 mg/dL within 48 hours
   b. An increase in SCr to ≥1.5 times baseline within the prior 7 days
   c. A urine volume of <0.5 mL/kg/h for 6 hours
   d. An increase in SCr to ≥1.5 times the upper limit of the "normal" range as listed in the laboratory reference values

Answer: d is correct. The KDIGO classification defines AKI as 1) an increase in SCr ≥0.3 mg/dL within 48 hours; 2) an increase in SCr to ≥1.5 times baseline within the prior 7 days, or 3) a urine volume of <0.5 mL/kg/h for 6 hours. The upper limit of normal from a reference range should not be used in diagnosing AKI if the patient's baseline SCr level is known.

2. Common manifestations of myeloma-related kidney disease include all of the following *except*:

   a. Cast nephropathy
   b. Light chain deposition disease
   c. Thrombotic microangiopathy (TMA)
   d. Light chain amyloidosis

Answer: c is correct. The three most common manifestations of myeloma-related kidney disease include cast nephropathy, light chain deposition disease, and light chain amyloidosis. Other less common manifestations include heavy chain deposition disease, membranoproliferative glomerulonephritis from cryoglobulinemia, and fibrillary glomerulonephritis. TMA is not a common presentation.

3. Which of the following therapies has shown efficacy in the treatment of HSOS after stem cell transplant?

   a. Heparin
   b. Defibrotide
   c. Tissue plasminogen activator (tPA)
   d. Plasmapheresis

Answer: b is correct. Heparin has been used for prophylaxis of HSOS with mixed results. Both heparin and tPA have unacceptable bleeding risks when used for treatment of HSOS. Defibrotide, an oligonucleotide that has antithrombotic and profibrinolytic properties with minimal anticoagulant effects, has shown promise in the treatment of patients with severe HSOS. Plasmapheresis has no role in the treatment of HSOS.