Acute Kidney Injury in the Cancer Patient

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Acute kidney injury (AKI) is a frequent and significant complication of cancer and cancer therapy. Cancer patients frequently encounter risk factors for AKI including older age, CKD, prerenal conditions, sepsis, exposure to nephrotoxins, and obstructive physiology. AKI can also be secondary to paraneoplastic conditions, including glomerulonephritis and microangiopathic processes. This complication can have significant consequences, including effects on patients' ability to continue to receive therapy for their malignancy. This review will serve to summarize potential etiologies of AKI that present in patients with cancer as well as to highlight specific patient populations, such as the critically ill cancer patient.

Key Words: Acute renal failure, AKI, Oncology, Nephrotoxins, Malignancy

Introduction and Epidemiology

Acute kidney injury (AKI) is a significant complication in patients with cancer and is associated with high morbidity and mortality. Rates of AKI vary in cancer patients on the basis of several factors, including type of malignancy (either solid tumor or hematologic), severity of malignancy, associated complications such as critical illness, and types of supportive or interventional therapy given to the patient. The largest cohort study of Danish cancer patients documented the highest rates of AKI in patients with kidney cancers at 44%, myeloma at 33% and liver cancer at 31.8%.[1] Patients with leukemia are also at high risk for AKI, with the Danish cohort study documenting a rate of 27.5%.[1] Another study including patients with high-risk myelodysplastic syndrome to patients with acute myelogenous leukemia documented an AKI rate of 36% in a 537-patient study.[2]

Among critically ill cancer patients, the rate of AKI is between 12% and 49%, with 9% to 32% of patients requiring renal replacement therapy.[3-6] These rates are higher in critically ill cancer patients than in other noncancer patient populations of similar severity of illness.[3,7,8] In critically ill patients with cancer, AKI usually does not occur in isolation; rather, it occurs in the setting of multiple organ dysfunction. Among patients with cancer and critical illness who develop AKI, outcomes are worse than other populations.[6,7,9] Mortality rates range from 72% to 85% when renal replacement therapy is needed.[3] The most common cause of AKI in patients with critical illness is sepsis.[10,11] In these patients with critical illness, AKI due to medications or secondary to the malignancies is also seen.[6] In a recent study of 200 patients with high-grade hematological malignancies and AKI, 68.5% had AKI according to the RIFLE criteria. Of all cases of AKI, 91.4% of these cases were due to 5 causes: hypoperfusion, tumor lysis syndrome, acute tubular necrosis (ATN), nephrotoxins and hemophagocytic lymphohistiocytosis.[12]

The outcomes of cancer patients with AKI are affected by several factors. Some cancer chemotherapeutic agents are cleared by the kidney. AKI alters the pharmacokinetics of these agents, which may lead to toxic levels. On the other hand, AKI requiring dialysis may lead to subtherapeutic levels of cancer drugs and potentially ineffective cancer treatment. In addition, dose-related adjustments of ancillary drugs, such as antibiotics and narcotics, may be necessary in patients with AKI. Toxic doses or inadequate doses may lead to adverse outcomes (Table 1). Thus, despite considerably improved chemotherapeutic agents, AKI may limit the efficacy of these improved agents. Kidney function should be closely monitored, and when possible, drugs with lower kidney toxicity or without kidney toxicity should be considered.[13,14] A major limitation in patients receiving dialysis is that the information on the pharmacokinetics of drug distribution affected by dialysis is limited. Another major factor affecting the outcomes of cancer patients is frequent association between critical illness and multiorgan dysfunction. Mortality rates in patients with multiorgan dysfunction increase with the number of affected organs.[15] In an observational study of 3591 critically ill patients requiring continuous renal replacement therapy, there was 90% and 100% mortality in patients with 4 and 5 dysfunctioning organs, respectively.[15] Other factors contributing to poor outcomes in cancer patients with AKI include altered nutritional status and immunity and infections related to dialysis access.

Some studies have documented a greater than 80% recovery of kidney function and 94% rate of dialysis independence if the cancer patient survives their critical illness.[6] Certain patient characteristics, including age, performance status, and available critical illness severity scoring systems, may help identify patients who would benefit from more aggressive management.[16-18]

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This review serves to summarize the different causes of AKI in cancer patients and to highlight several concerns specific to this patient population, including disease-related complications and nephrotoxicity with chemotherapy agents. We will avoid or minimize discussions related to myeloma-associated kidney disease, hematopoietic stem cell transplant-associated kidney disease, and tubulointerstitial lesions associated with cancer chemotherapy because these areas are covered in detail in other articles in this issue.

Etiologies of AKI

AKI seen in cancer patients can be categorized as having prerenal, intrarenal, or postrenal etiologies (Table 2).[19] These patients are at increased risk for AKI because of several factors related to older age, preexisting CKD, associated comorbidities, and coexisting drug therapies (Table 3).

Prerenal AKI

Prerenal AKI is frequently seen in cancer patient populations. In these patients, prerenal AKI may be due to true intravascular volume depletion, such as in the setting of sepsis, vomiting, or diarrhea.[6] In some cases medications may lead to mucositis and reduced oral intake, which can lead to prerenal AKI. In septic patients, hypotension and vasodilation due to sepsis or pharmacological interventions using vasoconstrictors, such as norepinephrine or vasopressin, may lead to hypoperfusion and prerenal AKI. Prerenal azotemia can also be seen in the setting of complications of malignancies, such as sinusoidal obstruction disease.[17] Hypercalcemia, which is seen in 20% to 30% of malignancies, can lead to a prerenal state because of the effects of hypercalcemia inducing kidney vasoconstriction as well as volume depletion from natriuresis and diuresis.[20] Finally, medications such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or nonsteroidal anti-inflammatory agents used for the malignancy or other medical conditions, such as hypertension or congestive heart failure, can lead to prerenal AKI. Consideration should be given to the risk-benefits of continuing these medications in patients with cancer who are at risk for prerenal AKI.[21]

CLINICAL SUMMARY

- AKI is common in patients with cancer, with overall rates and etiologies varying greatly based on the type of cancer and other comorbidities.
- Drug-induced AKI can be seen with therapeutic agents used in treatment of cancer, contrast agents, and drugs used in the treatment of the patient's co-morbid illnesses.
- AKI in the critically ill cancer patient is most commonly caused by sepsis, with prognosis affected by the patient's overall clinical status.

Postrenal AKI and Obstruction

Postrenal AKI due to obstructive processes is seen more commonly in malignancies than in the general population.[19] Postrenal AKI is commonly due to bladder outlet obstruction and ureteral obstruction. The most common solid organ malignancies causing obstructive processes include bladder, prostate, uterus, and cervix malignancies. Ureteral obstruction can also occur in these settings, as well as because of external compression from retroperitoneal lymphadenopathy. Diagnosis of obstructive uropathy may be difficult, and the diagnosis should always be suspected in patients with cancer. Anuria, flank pain, a palpable mass, or a palpable bladder should raise suspicion for the diagnosis of obstruction. However partial obstruction may lead to AKI without anuria. Laboratory tests demonstrating hyperkalemia with a nonanion gap metabolic acidosis is suggestive of a renal tubular acidosis associated with obstruction.[22]

Postrenal AKI is associated with a bland urine sediment, which may contain crystals or blood. Diagnosis of obstructive uropathy can be confirmed through diagnostic imaging. Imaging can be performed by ultrasound or computed tomography (CT) scan and most commonly will show hydronephrosis and/or hydroureter. The utility of ultrasound relates to its diagnostic yield in high-risk patients, rapid diagnosis, simplicity, noninvasiveness, and cost-effectiveness.[23] CT scans have the benefit of being able to better visualize other pelvic organs.[24] Obstructive AKI can present in the absence of hydronephrosis or hydroureter in the setting of retroperitoneal fibrosis, in early obstruction as a result of the malignancy itself, or as a complication of treatment of malignancy. Radiation therapy of the abdomen and pelvis can lead to retroperitoneal fibrosis. Treatment of obstructive AKI involves relief of obstruction by percutaneous nephrostomy or stenting. Recovery depends on the severity and duration of obstruction.

Intrinsic Kidney Disease

Intrinsic causes of AKI in cancer patients include primary glomerular disease, ATN due to toxins or ischemia, infiltrative processes, and microangiopathic processes.[16,19,21] These disease states may be secondary to either the primary disease process or its treatment. It is important to consider the patient's malignancy and any chemotherapeutic agents the patient has received when forming the patient's differential diagnosis.

Glomerulonephritis

Glomerular processes seen in malignancies include antineutrophil cytoplasmic antibody (ANCA) vasculitis,