Onco-Nephrology: AKI in the Cancer Patient

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Summary
AKI is common in patients with cancer, and it causes interruptions in therapy and increased hospital length of stay, cost, and mortality. Although cancer patients are susceptible to all of the usual causes of AKI in patients without cancer, there are a number of AKI syndromes that occur more frequently or are unique to this patient population. AKI also confers substantially increased risk of short-term death, and the ability to reverse AKI portends a better outcome in some cancers, such as multiple myeloma. Several trends in oncology, including increased survival, better supportive care, older patients who have received multiple chemotherapy regimens, and new therapeutic options, are driving an increase in the numbers of cancer patients who develop AKI. As a result, nephrologists should be increasingly familiar with the diagnosis, management, and treatment of AKI in this setting. Here, we summarize recent data on epidemiology of AKI in cancer patients, describe the most common AKI syndromes in this population, and highlight emerging areas in the growing field of onconephrology.


Introduction
The increasing life expectancy of cancer patients and accelerating pace of new treatment discoveries over the last decade have been welcome news for patients diagnosed with malignancy. However, in 2008, there were almost 12 million patients alive with cancer in the United States alone, and cancer remains the second leading cause of death (1). AKI is an important complication of cancer and its treatment. With increasingly complex cancer treatment protocols and drugs and the growing emphasis on a team approach to cancer care, it is critical for nephrologists to stay informed about new developments in the new field of onco-nephrology (2).

Epidemiology of AKI in Cancer
Historically, relatively few large studies have analyzed the epidemiology of AKI among cancer patients, but recent investigations have focused on this question. In a Danish population-based study, 1.2 million people were followed from 1999 to 2006. During this time, there were 37,267 incident cancer patients, and 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 (3). Kidney cancer, multiple myeloma, and liver cancer had the highest 1-year risks of AKI at 44.0%, 33.0%, and 31.8%, respectively. The overall survival for patients with cancer has improved dramatically for certain specific cancers over the last 10 years. Two of these cancers for which recent therapeutic advances have translated into longer progression-free and overall survival include renal cell carcinoma and multiple myeloma (4,5). Because these cancers are both cancers with high AKI risk, it will be important to track the changing incidence of AKI in these groups over time.

Other subgroups of cancer patients are at especially high risk of AKI, such as those patients with acute lymphoma or leukemia undergoing induction chemotherapy. In a series of 537 patients with either acute myelogenous leukemia or high-risk myelodysplastic syndrome undergoing induction, 36% of patients 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 renal replacement therapy experienced mortality of 61.7% (95% confidence interval=50–74%) over the same frame (6).

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 chronic kidney disease at 1 year (7). Although the risk of AKI with partial nephrectomy has not been studied, the risk of CKD after partial nephrectomy is much lower compared with radical nephrectomy (8), and recent evidence suggests better cardiovascular outcomes and overall survival in partial nephrectomy (9). It is reasonable to assume that AKI rates during and after partial nephrectomy will also be lower than radical nephrectomy as a consequence of greater nephron mass. Despite equivalent cancer outcomes with reduced morbidity and possibly, mortality of partial nephrectomy, unnecessary radical nephrectomies are still being performed. In tertiary care centers, 30%–65% of solitary cortical tumors are resected by partial nephrectomy; however, partial nephrectomy is used only 7% of the time for the same tumors in the community (10,11). One explanation advanced for this troubling trend is that surgeons have converted from open to laparoscopic radical nephrectomies rather than from open radical nephrectomies to partial nephrectomies (12). The association between AKI and hematopoietic cell transplantation (HCT) has been studied in depth and reviewed recently (13,14). In particular, AKI in HCT recipients is a risk factor for both
short- and long-term mortality, with a graded relationship between AKI severity and mortality risk.

AKI is common in hospitalized patients and also correlates with increased length of stay, cost, and mortality just as it does in patients with AKI who do not have cancer. The work by Candrilli et al. (15) analyzed the 2004 Nationwide Inpatient Sample for patients with hematologic malignancies. These authors 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) (15). The average length of stay and costs among these groups were 7.4, 12.2, and 17.6 days and $13,947, $25,638, and $44,619, respectively (15).

The high mortality rate among cancer patients with severe AKI (requiring dialysis) has prompted some to question whether renal replacement therapy should be offered at all. However, where it has been studied, the data suggest that cancer patients with AKI requiring dialysis in the intensive care unit have similar mortality to patients without cancer (16,17). Moreover, although mortality is high, initiating renal replacement therapy for AKI in cancer patients does not condemn them to chronic dialysis in many cases. In one large series, only 5 of 22 patients that had dialysis-requiring AKI in the intensive care unit and survived to 6 months remained on dialysis (18).

Causes of AKI in the Cancer Patient
The initial approach to a cancer patient with AKI is not substantially different than the approach to any other patient. A detailed history and physical exam remain the cornerstones of diagnosis, with laboratory analysis, urinary sediment examination, and imaging providing additional information. In formulating a differential diagnosis, however, a variety of AKI causes have a higher pretest probability in cancer patients. Below, we review AKI specific to cancer patients. Chemotherapy-induced AKI will not be reviewed here, because it is the subject of the work by Perazella et al. (19).

Prerenal Causes
Patients being treated for cancer frequently develop volume depletion related to nausea, vomiting, or diarrhea as a toxicity of chemotherapy. They may ingest nonsteroidal anti-inflammatory medications. Many patients are anemic. As with the general population, there is also a high frequency of diuretic, angiotensin-converting enzyme, or receptor blocker use. All of these factors make prerenal azotemia a common diagnosis among cancer patients. Whether the long-term benefits of angiotensin converting enzyme inhibitors and angiotensin receptor blockers among hypertensive and/or diabetic cancer patients are worth the increased short-term risk of AKI during cancer treatment requires investigation.

Hypercalcemia is a frequent complication in cancer, occurring in 20%–30% of patients over the course of disease (20). Hypercalcemia causes AKI by means of direct renal vasoconstriction and natriuresis-induced volume depletion, and it is reviewed elsewhere in this issue.

Intrinsic Causes
Lymphomatous Infiltration of the Kidney. Lymphomatous infiltration of the kidneys (LIK) is relatively common and an underrecognized complication of hematologic malignancies, although it is usually subclinical (21). Approximately one-half of patients with non-Hodgkin’s lymphoma develop extranodal disease, and the largest case series to date found that 34% of lymphoma patients had parenchymal kidney invasion but only 14% had been diagnosed before death (22). Scant data exist to identify the incidence of LIK according to lymphoma classification, although most subtypes have been reported at the case report level. Although enlarged kidneys on imaging, AKI, and subclinical proteinuria are common findings, LIK is almost always diagnosed by renal biopsy (23). For indolent cancers such as chronic lymphocytic leukemia, which is often not treated unless there is evidence of end-organ damage, diagnosis of LIK may be the trigger to start treatment. Management is focused on treatment of the primary malignancy, and renal function may improve after therapy (Figure 1).

Cast Nephropathy. Evidence of renal insufficiency is identified in approximately 20%–40% of patients newly diagnosed with multiple myeloma, and it is an independent predictor for increased morbidity and mortality (24,25). Cast nephropathy (also known as myeloma kidney) is the most common presentation of AKI related to multiple myeloma and the most common histologic lesion in renal biopsies of patients with monoclonal gammopathies (26). Under normal physiologic conditions, immunoglobulin light chains are freely filtered by the glomerulus and taken up by tubular cells by cubulin/megalin receptors and clathrin-dependent endocytosis, where they are subsequently degraded in lysosomes (Figure 2) (27). The increased production of light chains by neoplastic plasma cell populations overwhelms the proximal tubular capacity to perform this function, and excess light chains bind to Tamm–Horsfall protein in the distal tubule, causing obstruction and a reduction in GFR. Factors that promote cast formation include a heavy load of serum-free light chains (SFLC) delivered to the distal tubule, acidic urine, concurrent treatment with furosemide or nonsteroidal anti-inflammatory drugs, dehydration, intravenous contrast, and hypercalcemia (28).

If treated early, cast nephropathy has the potential to be reversed, and therefore, prompt treatment measures should be taken on diagnosis. Patients should be adequately volume-expanded with intravenous fluids such as isotonic saline or sodium bicarbonate, although this process results in a small decrease in light-chain concentration at best. An optimal choice of fluids has not been supported by any substantial evidence. Urinary alkalization may help to increase the solubility of SFLC. Antimyeloma agents (bortezomib, dexamethasone, thalidomide, and lenalidomide) should be initiated as soon as safely possible to try to decrease SFLC production, because an early reduction of SFLC portends improved renal recovery in cast nephropathy (29). Nephrotoxic agents, including nonsteroidal anti-inflammatory drugs, intravenous contrast, loop diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aminoglycosides, should be avoided.

The role of plasmapheresis in the management of cast nephropathy continues to be a topic of considerable debate. Given the established role of myeloma light chains in causing renal injury, the clinical benefit of using plasmapheresis to reduce the burden of light chains has been investigated in
performed before the introduction of proteasome inhibitors (e.g., bortezomib) and SFLC assays, and the role of plasmapheresis in the setting of these important developments may warrant additional investigation. In an analysis of 14 patients with newly diagnosed or relapsed multiple myeloma and cast nephropathy treated at the Mayo Clinic, treatment with bortezomib plus plasmapheresis resulted in normalization of serum creatinine levels in 43% of patients, with another 43% of patients achieving >50% reduction in serum creatinine or freedom from hemodialysis within 6 months of initiation (33). SFLCs were reduced by a mean of 74.6% on discontinuation of plasmapheresis and 96.5% by 3 months after treatment was initiated. Based on these data, the work by Cagnoli et al. (34) concluded that there may be a role for plasmapheresis combined with bortezomib in reversing AKI secondary to cast nephropathy, but additional studies are needed.

The recent development of high cutoff (HCO) dialyzers used with extended hemodialysis sessions offers an alternative approach to the efficient removal of SFLC (Figure 3) (39). In a study of 19 patients with biopsy-proven cast nephropathy treated with conventional chemotherapy regimens and extended hemodialysis using the Gambro HCO 1100 dialyzer (Gambro Dialysatoren GmbH, Hechingen, Germany), 13 patients experienced an early, sustained reduction in SFLC (median=85%) and became dialysis independent at a median of 27 days (39). The remaining six patients had an interruption in chemotherapy, five of whom did not recover renal function. Renal recovery was correlated with improved survival. One small case control study has also shown improved rates of renal recovery and dialysis discontinuation with HCO hemodialysis (40). The promising benefits of HCO hemodialysis are being tested combined with bortezomib-based chemotherapy in the multicenter RCT European Trial of Free Light Chain Removal by Extended Hemodialysis in Cast Nephropathy.

Monoclonal gammopathies in the absence of a myeloma diagnosis are also an important cause of AKI, but a discussion of the spectrum of paraprotein-mediated renal disease is beyond the scope of this article. Additional information can be found in recent reviews (41,42).

**Tumor Lysis Syndrome.** Considered an oncologic emergency, tumor lysis syndrome (TLS) is a common cause of AKI in the patient with malignancy. TLS occurs when tumor cells release their intracellular contents into the bloodstream, resulting in a constellation of metabolic disturbances including hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. These electrolyte abnormalities also put patients with TLS at risk for cardiac arrhythmias, seizures, and death. Although TLS can occur spontaneously, it is most often seen as a consequence of treatment of malignancy by standard chemotherapy, radiation, corticosteroids, immunotherapy, monoclonal antibodies, and other targeted therapies. Malignancies with high tumor burden, rapid cell turnover, and increased sensitivity to chemotherapy (e.g., acute leukemias and high-grade lymphomas) are at highest risk for developing TLS; however, TLS has recently been associated with tumors that were previously thought to be low risk, such as hepatocellular carcinoma, endometrial cancer, non–small cell lung cancer, colon carcinoma, chronic myelogenous leukemia, and chronic lymphocytic leukemia (43). The development of highly potent

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**Figure 1.** Lymphomatous infiltration of the kidney. (A) A 63-year-old man with a history of B cell chronic lymphocytic leukemia not on therapy developed AKI with a serum creatinine of 3.2 mg/dl and leukocytosis of 87,000. Renal biopsy disclosed diffuse lymphomatous infiltration of the kidney characterized by monomorphic cellular infiltrates throughout the interstitium visible on hematoxylin and eosin stain. (B) The cellular infiltrate was positive for CD20 (brown stain), confirming the B cell identity of the infiltrate and consistent with the patient’s B cell leukemia. (C) The patient was started on fludarabine + rituxan therapy, and serum creatinine improved to 1.8 mg/dl, where it has remained for 2 years. Fludar, fludarabine; ritux, rituxan. Images courtesy of Helmut Rennke.

Several studies, including three randomized controlled trials (RCTs) (30–37). One of these RCTs showed a survival benefit and improved renal function in the plasmapheresis group; however, patients in the plasmapheresis group received hemodialysis, whereas those patients in the control group received peritoneal dialysis (31). The largest of these RCTs randomized 104 patients with myeloma and AKI to conventional therapy with or without five to seven plasma exchanges over 10 days and found that plasmapheresis did not significantly reduce death, dialysis dependence, or GFR < 30 ml/min per 1.73 m² (32). Two limitations of this study were that neither renal biopsy data nor quantitation of SFLC was provided. A recent systematic review by Gupta et al. (38) concluded that plasmapheresis does not offer a significant benefit over chemotherapy alone in terms of survival, discontinuation of dialysis, or improvement in renal function. However, all of these studies were
**Figure 2.** Cast nephropathy. Schematic diagram illustrating the pathophysiology of AKI in cast nephropathy. Free light chains filtered by the glomerulus are taken up by proximal tubular epithelial cells through the cubulin–megalin receptor complex and clathrin-dependent endocytosis, where they are metabolized in lysosomes. Excess free light chains overwhelm lysosomal capacity, leading to activation of redox pathways, increased NF-κB and mitogen-activated protein kinase expressions, and production of proinflammatory, profibrotic cytokines. Light chains bind to Tamm–Horsfall protein in the lumen of the distal tubule, where they precipitate and form casts. CCL2, C–C motif chemokine 2; MAPK, mitogen-activated protein kinase; THP, Tamm–Horsfall protein. Modified from ref. 27, with permission.

**Figure 3.** Comparison of sieving coefficients between high cutoff (HCO) and high-flux membranes. Clearance of higher molecular weight molecules, including light chains, is greater with HCO dialyzers compared with conventional high-flux membranes. Reprinted from ref. 69, with permission.
chemotherapeutic agents such as flavopiridol (a cyclin-dependent kinase inhibitor used to treat chronic lymphocytic leukemia) has also led to a markedly increased risk for developing TLS (44). The pathophysiology of AKI in TLS involves the formation of crystals comprised of uric acid, calcium phosphate, and/or xanthine, which can lead to intratubular obstruction and inflammation and a reduction in GFR. In addition, hyperuricemia can cause AKI through crystal-independent mechanisms, such as renal vasoconstriction, reduced renal blood flow, reactive oxygen species, and inflammation (43). The management of TLS is reviewed elsewhere (19).

Postrenal Causes of AKI
Obstruction is an important cause of AKI and should always be considered in the cancer patient. It is most common in cancers of the prostate, bladder, and kidney or secondary to extrinsic compression of the urinary outflow tract from both primary and metastatic abdominal or pelvic malignancies. Many renal cell carcinoma patients only have one kidney and therefore, are susceptible to AKI from unilateral ureteral obstruction. Diagnosis of obstruction is usually established radiographically by the presence of hydrenephrosis on either abdominal ultrasonography or computed tomography, but false-negative results can be seen in the setting of hypovolemia, early or partial obstruction, or obstruction caused by retropitoneal fibrosis. Interventions to relieve the obstruction include placement of ureteral stents and percutaneous nephrostomy tubes, which can lead to reversal of renal impairment.

AKI after HCT
Since the 1960s, HCT, formerly known as bone marrow transplantation, has been used to treat a number of malignant and nonmalignant diseases. Although HCT offers a potential cure for several conditions that may be refractory to chemotherapy, it is associated with a host of organ toxicities, with AKI being one of the most common serious complications of HCT (14). The incidence and timing of AKI after HCT vary according to the type of transplant. The original report by Zager (45), which analyzed 272 patients undergoing myeloablative HCT (89% allogeneic and 11% autologous), found that 53% of patients developed AKI (defined as doubling of serum creatinine), with one-half of these patients requiring dialysis. This remarkably high incidence of AKI in myeloablative allogeneic HCT has been confirmed in several more recent studies (46–49). In nonmyeloablative allogeneic HCT, which employs a less toxic conditioning regimen and has fewer complications, the incidence of AKI is lower (29%–40.4%) (48,50,51). Myeloablative autologous HCT has the lowest incidence of AKI (22%) (52,53), a difference that can be attributed to the lack of graft versus host disease (GVHD), the absence of calcineurin inhibitors, and more rapid engraftment in this population. Most cases of AKI occur within the first 100 days after HCT, with an earlier onset in myeloablative (7–40 days) compared with nonmyeloablative regimens (22–60 days) (14). Overall mortality rates in patients with AKI range from 37% to 46% and are as high as 88% in patients requiring dialysis (46,54). Importantly, AKI after HCT predicts the subsequent development of CKD in both myeloablative and nonmyeloablative HCT (14).

The causes of AKI after HCT can be divided into those causes occurring early after HCT (within the first 30 days) and those causes occurring later (>3–4 months) (Table 1). During the peritransplant period, AKI is most commonly caused by sepsis, hypotension, and exposure to nephrotoxic agents (methotrexate, amphotericin B, acyclovir, aminoglycosides, angiotensin-converting enzyme inhibitors, intravenous contrast, and calcineurin inhibitors), which predispose the patient to acute tubular necrosis (45). In addition, the administration of antibiotics and/or allopurinol can cause acute interstitial nephritis. TLS can occur as a result of the conditioning regimen, although the incidence of this occurrence is low in this population (45). Hepatic sinusoidal obstruction syndrome presents early post-HCT with clinical and laboratory features similar to hepatorenal syndrome. Late-onset AKI after HCT has a more limited differential diagnosis, and it is usually attributed to thrombotic microangiopathy or calcineurin inhibitor toxicity (45).

Calcineurin Inhibitor Toxicity
Calcineurin inhibitors (cyclosporine and tacrolimus) are widely used for prevention of GVHD in patients undergoing allogeneic HCT. Both cyclosporine and tacrolimus, in either oral or parenteral formulation, can acutely induce renal vasoconstriction and reduce GFR in a dose-dependent manner. Calcineurin inhibitor nephrotoxicity plays a more significant role in the development of AKI in nonmyeloablative than myeloablative HCT, where it has not been associated with AKI in multiple studies (55). In addition to their acute nephrotoxicity, calcineurin inhibitors can also cause progressive, irreversible CKD and are a risk factor for the development of HCT-associated thrombotic microangiopathy (55). Routine monitoring of serum creatinine and plasma drug levels (cyclosporine=150–400 ng/ml; tacrolimus=15 ng/ml) (56) is important in determining when appropriate dose reductions are necessary to help preserve renal function.

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<th>Table 1. Causes of AKI after hematopoietic cell transplant</th>
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<td>Sepsis</td>
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<td>Hypotension</td>
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<td>Hypovolemia (vomiting and diarrhea)</td>
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<td>Nephrotoxic agents</td>
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<td>Acyclovir</td>
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<td>Allopurinol</td>
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<td>Amphotericin B</td>
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<td>Angiotensin-converting enzyme inhibitors</td>
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<td>Calcineurin inhibitors</td>
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<td>Contrast dye</td>
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<td>NSAIDs</td>
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<td>Tumor lysis syndrome</td>
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<td>Hepatic sinusoidal obstruction syndrome</td>
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<td>Late onset (&gt;3 months)</td>
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<td>Thrombotic microangiopathy</td>
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<td>Calcineurin inhibitor toxicity</td>
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NSAIDS, nonsteroidal anti-inflammatory drugs.
Hepatic Sinusoidal Obstruction Syndrome (Veno-Occlusive Disease)

Hepatic sinusoidal obstruction syndrome (SOS), previously known as veno-occlusive disease, is the constellation of tender hepatomegaly, fluid retention, weight gain, and jaundice that occurs after the administration of high-dose conditioning regimens, including cyclophosphamide, busulfan, and/or total body irradiation (57). The pathophysiology of SOS involves damage to hepatic sinusoidal endothelial cells in zone 3 of the hepatic acinus, which leads to sinusoidal thrombosis and obstruction and portal hypertension. Although SOS has historically been reported in 5%–60% of patients, a recent review of studies performed between 1979 and 2007 found that the overall mean incidence of SOS was 13.7% (58). SOS occurs more commonly after myeloablative allogeneic HCT than after autologous HCT (59), and it is essentially nonexistent with nonmyeloablative regimens. Risk factors for developing SOS include older age, pre-existing liver disease, medications (methotrexate, ifosfamide, sirolimus, and norethisterone), and certain conditioning agents (cyclophosphamide and busulfan) (45,60).

AKI develops in approximately 50% of patients with SOS and is clinically indistinguishable from the hepatorenal syndrome. Patients initially present with sodium retention, weight gain, peripheral edema, and ascites accompanied by hepatic dysfunction and hyperbilirubinemia. AKI ensues 10–16 days post-HCT, with approximately one-half of patients requiring dialysis (45). Patients typically have low blood pressures and are frequently hyponatremic, and most have persistently low fractional excretion of sodium. Urinalysis shows variable proteinuria and/or hematuria; most have persistently low fractional excretion of sodium. Renal biopsies and autopsies performed in patients with SOS have not shown evidence of structural kidney lesions, confirming the notion that AKI is likely hemodynamically mediated (54). Mortality is 37% in those patients experiencing a doubling of serum creatinine and as high as 84% in those patients requiring dialysis (57).

More than 70% patients with SOS will 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 (60). For patients with severe SOS, there are no highly effective treatments, although the best results have been achieved with defibrotide, a single-stranded oligodeoxyribonucleotide with antithrombotic and profibrinolytic properties that has a 46% complete response rate (61). Infusion of heparin and/or unfractionated heparin administered immediately before induction therapy may also be moderately successful as preventive measures.

Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) is a common cause of late-onset AKI in patients who have undergone HCT. Previously known as bone marrow transplant nephropathy or radiation nephropathy, TMA after HCT resembles the hemolytic-uremic syndrome and usually occurs 20–99 days post-transplant. The diagnosis of TMA can be challenging, because characteristic features such as anemia, thrombocytopenia, and renal insufficiency are commonly present in the HCT patient population for other reasons, and evidence of schistocytes or elevated serum lactate dehydrogenase levels is also not entirely reliable (62). Hyper tension is often present. Urinalysis can be normal or reveal variable proteinuria and/or hematuria, and cellular casts may be seen on urine sediment. Renal biopsy is rarely 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 (Figure 4) (63).

The pathogenesis of TMA after HCT is not well understood, but damage to renal endothelial cells likely plays a central role. The conditioning regimen, particularly the use of total body irradiation, is a primary cause of renal endothelial damage, with post-HCT factors such as GVHD, infections, and medications (such as the calcineurin inhibitors) playing a later modulatory role (64). Such strategies may prevent the need for anticoagulation, and slow radiation administration have been proposed to reduce radiation injury (45). However, these approaches run the risk of decreasing the effectiveness of tumor cell eradication. The management of HCT-associated TMA is otherwise largely supportive. Calcineurin inhibitors are typically 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 (65). Substitution of calcineurin inhibitors with daclizumab, a humanized monoclonal antibody to the α-chain of the IL-2 receptor, has been shown to improve TMA in patients with both GVHD and TMA (66). Rituximab, a monoclonal

Figure 4. | Thrombotic microangiopathy after hematopoietic cell transplantation. (A) A 25-year-old woman was diagnosed with high-risk acute myelogenous leukemia, underwent induction chemotherapy, and experienced a slow hematologic recovery. She subsequently underwent allogeneic double-cord blood hematopoietic cell transplantation; 6 months later, her serum creatinine rose from 1.2 to 2.4 mg/dl in association with new hypertension, thrombocytopenia, and evidence of microangiopathic hemolysis. Kidney biopsy revealed diffuse and severe endothelial damage with double contours and occlusion of capillary lumens (periodic acid–Schiff stain). (B) There is marked endothelial swelling (endotheliosis) with fragmented red blood cells visible in capillary lumens and the damaged mesangium (arrows, hematoxylin and eosin stain). (C) Electron microscopy of a single glomerular capillary loop reveals expansion of the subendothelial space by electron lucent debris (asterisks), narrowing of the capillary lumen, and loss of endothelial fenestrations. Images courtesy of Helmut Rennke.
antibody against CD20, and defibrotide have also shown effectiveness in treating HCT-associated TMA in small, uncontrolled studies (67). Given its important role in the treatment of non-HCT-associated TMA, plasmapheresis is sometimes used to treat HCT-associated TMA, but there is no established proof of benefit with this approach (62). Other experimental therapies for TMA under investigation have focused on attenuating inflammatory endothelial injury and include 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, prostacyclin analogs, endothelin receptor antagonists, antithrombin III, IgG, and anti-TNF agents (65,67). 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 (65). 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 (65).

GVHD

GVHD, the most common complication of HCT, increases the risk of AKI in both myeloablative and nonmyeloablative regimens (14). Renal disease associated with GVHD can be directly caused by cytokine- and immune-related injury and includes glomerular disease (most commonly membranous nephropathy) as well as tubulitis (14,68). Prophylaxis against GVHD with calcineurin inhibitors can also contribute to AKI as previously discussed. Patients with GVHD are at higher risk of developing TMA and its associated renal complications (67).

Conclusions

AKI is common among cancer patients. Both nephrologists and oncologists need to be aware of the unique causes of AKI in this population and its optimal management. The growing number of cancer survivors combined with new therapies and an emphasis on team-based cancer care mean that the field of onco-nephrology will continue to grow, hopefully improving outcomes for cancer patients with kidney complications.

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Disclosures

None.

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