

Acute kidney injury and CKD associated with Hematopoietic stem cell transplantation

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Introduction

- Hematopoietic stem cell transplantation is a life-saving therapy for many patients with cancer, as well as patients with some nonmalignant hematologic disorders, such as aplastic anemia, sickle cell disease, and certain congenital immune deficiencies. Kidney injury directly associated with stem cell transplantation includes a wide range of structural and functional abnormalities, which may be vascular (hypertension, thrombotic microangiopathy), glomerular (albuminuria, nephrotic glomerulopathies), and/or tubulointerstitial. AKI occurs commonly after stem cell transplant, affecting 10%–73% of patients. The cause is often multifactorial and can include sepsis, nephrotoxic medications, marrow infusion syndrome, hepatic sinusoidal obstruction syndrome, thrombotic microangiopathy, infections, and graft versus host disease. The risk of post-transplant kidney injury varies depending on patient characteristics, type of transplant (allogeneic versus autologous), and choice of chemotherapeutic conditioning regimen (myeloablative versus nonmyeloablative).

- Importantly, AKI is associated with substantial morbidity, including the need for KRT in approximately 5% of patients and the development of CKD in up to 60% of transplant recipients. AKI has been associated universally with higher all-cause and nonrelapse mortality regardless of transplant type, and studies have consistently shown extremely high (>80%) mortality rates in those patients requiring acute dialysis. Accordingly, prevention, early recognition, and prompt treatment of kidney injury are essential to improving kidney and patient outcomes after hematopoietic stem cell transplantation, and for realizing the full potential of this therapy

Types of Hematopoietic Stem Cell Transplantation

- Hematopoietic stem cell transplantation involves upfront chemotherapy with or without radiotherapy, followed by bone marrow rescue by engraftment of stem or progenitor cells, which are harvested from bone marrow, peripheral blood, or umbilical cord blood (Table 1). Stem or progenitor cells may come from the affected patient (autologous) or from a sibling or unrelated donor (allogeneic). In both myeloablative allogeneic and autologous transplantation, high-dose chemotherapy and radiation are given to eradicate the bone marrow and underlying cancer. Those patients not eligible for aggressive myeloablative therapy because of age or comorbidities may still be candidates for nonmyeloablative (“miniallo”) transplants, which utilize lower-intensity (less toxic) conditioning regimens..

- The goals of nonmyeloablative regimens are not to eradicate the bone marrow or malignant cells, but to provide sufficient immunosuppression to permit the engraftment of transplanted stem cells, which then target tumor cells (“graft versus tumor” effect). Importantly, both myeloablative allogeneic and nonmyeloablative allogeneic transplantation require the use of post-transplant immunosuppression, often with a calcineurin inhibitor, for prevention of GVHD. Autologous transplantation does not require GVHD prophylaxis

Table 1. Types of hematopoietic stem cell transplant

- **Source of stem or progenitor cells**
 - Bone marrow
 - Peripheral blood
 - Umbilical cord blood
- **Type of donor**
 - Autologous (patient)
 - Allogeneic (relative [usually a nonidentical sibling] or unrelated donor; requires prophylaxis against GVHD, often in the form of a CNI)
 - Syngeneic (identical twin)
- **Type of conditioning regimen**
 - Myeloablative (most toxic; aims to eradicate the bone marrow and underlying cancer)
 - Nonmyeloablative (least toxic; aims to provide sufficient immunosuppression to permit engraftment of transplanted cells, which target tumor cells [graft versus tumor effect])
 - Reduced-intensity conditioning (intermediate intensity)
- GVHD, graft versus host disease;
- CNI, denotes calcineurin inhibitor

Epidemiology of AKI

INCIDENCE AND OUTCOMES

- AKI is a common complication after stem cell transplantation, with varied incidences depending on the definition of AKI, chemotherapeutic conditioning regimen (myeloablative versus nonmyeloablative), and type of transplant (allogeneic versus autologous). In general, myeloablative regimens are associated with greater nephrotoxicity than nonmyeloablative regimens, and risk of AKI is higher with allogeneic compared with autologous transplantation

- In a landmark study analyzing 272 patients after myeloablative transplant (89% allogeneic, 11% autologous), 53% of patients developed AKI (defined as a doubling of serum creatinine); approximately half of these patients required dialysis . Subsequent studies published by Parikh et al. similarly demonstrated very high rates of AKI after myeloablative allogeneic transplantation. Importantly, myeloablative allogeneic therapy was associated with a greater incidence of severe kidney failure (73% versus 47%) and a four-fold greater need for dialysis (12% versus 3%) compared with patients in the nonmyeloablative group

- Incidence of AKI in the myeloablative group was 4.8-fold higher after controlling for baseline characteristics including age and comorbidities. These differences have been attributed to the greater toxic exposures associated with myeloablative conditioning. Autologous transplantation has the lowest incidence of AKI (approximately 20%)

- this has been ascribed to the absence of GVHD, lack of calcineurin inhibitor exposure, and more rapid engraftment (fewer cytopenias leading to less sepsis and nephrotoxic antibiotic exposure) . Recent data suggest that the incidence of AKI after stem cell transplantation is decreasing, potentially owing to the use of lower-dose myeloablative regimens and lower risks of sinusoidal obstruction syndrome, Gram-negative bacteremia, and severe GVHD, along with decreased exposure to amphotericin B . As with AKI incidence, the risk of requiring KRT after transplantation varies widely, with published rates ranging from 0% (autologous) to 33% (myeloablative allogeneic) . Overall, approximately 5% of patients develop AKI requiring hemodialysis

- AKI has been associated with higher all-cause and nonrelapse mortality, and AKI occurring before engraftment is associated with an inferior prognosis. Mortality is higher with worsening degrees of kidney failure regardless of transplant type, and studies have consistently shown extremely high (.80%) mortality rates in those patients requiring acute dialysis .

Risk Factors

- AKI generally occurs in the first month after myeloablative transplantation .During this early posttransplant period, patients are more susceptible to AKI because of the toxicities associated with the intense conditioning regimens used, including sepsis, hepatic sinusoidal obstruction syndrome, and medication-induced kidney injury .It has been suggested that the engraftment syndrome, which occurs within the first 30 days posttransplant and is characterized by fever, erythematous skin rash, and noncardiogenic pulmonary edema, is also linked to AKI. This syndrome is more common after autologous transplant, but can also occur after myeloablative and nonmyeloablative allogeneic transplant

- Reported risk factors for development of AKI after nonmyeloablative allogeneic transplantation include diabetes mellitus, receiving more than three previous courses of chemotherapy, and use of methotrexate for GVHD prophylaxis. GVHD itself is also a risk factor for AKI, but only after day 100, and cyclosporine levels have not been shown to be clearly predictive for development of AKI .However, the use of cyclosporine in patients with diabetes is strongly linked to a higher risk for AKI, especially during the first 100 days post-transplant

Pathophysiology of AKI

Sepsis

- Immunocompromised recipients may develop infections that lead to sepsis complicated by AKI .Sepsis-induced AKI occurs from systemic vasodilatation with hypotension and kidney hypoperfusion, cytokinerelated tubulointerstitial injury, and intrarenal endothelial dysfunction with capillary thrombosis. Nephrotoxic medications, such as aminoglycosides and vancomycin (often in combination with piperacillin-tazobactam), may contribute to sepsis-related AKI

Tumor Lysis Syndrome

- Patients with hematologic malignancies, and rarely solid cancers, may develop tumor lysis syndrome complicated by AKI. However, this is a rare complication after stem cell transplantation as the cancer is often eliminated by the time of transplant. When it occurs, AKI results from cytokine-related kidney damage, crystalline-induced tubular injury (hyperuricemia/hyperphosphatemia), or crystalindependent uric acid–related nephrotoxicity.

Nephrotoxic Medications

- Several antimicrobial agents are well known causes of AKI; mechanisms include direct kidney injury and idiosyncratic allergic responses leading to acute interstitial nephritis

- Aminoglycosides may cause AKI in at-risk patients. Underlying CKD, volume depletion, liver disease, exposure to other nephrotoxins, multiple versus single dosing aminoglycoside regimens, and prolonged exposure increase risk for AKI after stem cell transplantation. Classically, AKI develops after 7–10 days of drug exposure; however, tubular injury often occurs earlier. Tubulopathies such as proximal tubulopathy/Fanconi syndrome and Bartter-like syndrome may also develop

- Sulfonamides and ciprofloxacin may cause post-transplant AKI, especially in the setting of sepsis and volume depletion. Excessive drug dosing for underlying kidney function has been associated with crystalline-induced tubular injury. Acidic urine increases sulfonamide-induced crystal deposition within tubules, whereas alkaline urine increases ciprofloxacin-related crystal tubular deposition. Acyclovir, used for the prevention and treatment of certain viral infections in patients receiving stem cell transplant, has been associated with crystalline-related tubular injury and obstruction. However, with adequate hydration, appropriate dosing for level of kidney function, and slow intravenous infusion, this is quite rare

- The antifungal agents amphotericin B deoxycholate and the newer lipid-based (liposomal) preparations may cause AKI in patients who have other risk factors for AKI. These drugs cause AKI via kidney vasoconstriction and direct tubular toxicity (disruption of cell membranes), although the lipid-based preparations are less nephrotoxic. Nephrotoxicity is dose-related. Calcineurin inhibitors are used to prevent GVHD in allogeneic recipients and are associated with AKI. These drugs promote kidney arteriolar vasoconstriction through activation of the renin-angiotensin-aldosterone system and increase oxidative stress causing kidney endothelial damage, and are associated with TMA. Reninangiotensin-aldosterone system inhibition may be useful for prevention of calcineurin inhibitor nephrotoxicity

Marrow Infusion Syndrome

- The process of stem cell preservation, which includes exposure to various cryoprotectants such as DMSO, can cause red blood cell (RBC) lysis. Subsequent infusion of lysed RBCs during transplantation may cause fever, vomiting, and BP fluctuations, along with hemoglobin pigment nephropathy within 24–48 hours of transplantation (marrow infusion syndrome). AKI results from kidney vasoconstriction, direct hemoglobin cytotoxicity, and intratubular hemoglobin cast formation

Hepatic Sinusoidal Obstruction Syndrome

- Hepatic sinusoidal obstruction syndrome (formerly known as veno-occlusive disease) after stem cell transplantation is associated with AKI. It occurs within 30 days of transplant and is more common after allogeneic therapy .Published incidence from recent studies ranges from 2% (by updated European Society for Blood and Marrow Transplantation criteria) to 31% .Sinusoidal obstruction occurs from damage to sinusoidal endothelial cells and hepatocytes, which results in fibrous narrowing of small hepatic venules/sinusoids. Cytokine release and glutathione depletion may also cause hepatocellular necrosis and fibrosis. Pretransplantation cytoreductive regimens (busulfan, cyclophosphamide, and/or total body irradiation) are presumed triggers

- The novel antibody-drug conjugates gemtuzumab ozogamicin and inotuzumab, given before transplantation for the treatment of acute myelogenous leukemia and acute lymphoblastic leukemia, respectively, have been implicated in recent studies .Sinusoidal obstruction syndrome appears to be a variant of hepatorenal syndrome and is characterized by jaundice, painful hepatomegaly, and fluid retention .Patients are often diuretic resistant and spontaneous recovery is rare, with mortality rates approaching 80%, especially when dialysis is needed.

Acute TMA

- Acute transplant-associated TMA is characterized pathologically by endothelial cell swelling, fibrin thrombi within capillary loops and arterioles, fragmented RBCs, and thickened glomerular and arteriolar vasculature .Subclinical kidney disease, AKI, or CKD may result .It is unclear if TMA is a direct complication of transplantation or a manifestation of GVHD, infection, or drug toxicity

- Conditioning regimens and exposures may promote kidney endothelial injury with subsequent TMA. Recent studies also support that transplantation may unmask undiagnosed alternative complement pathway mutations, resulting in atypical hemolytic uremic syndrome; mutations in complement factor H, complement factor I, complement factor B, MCP/CD46, and C3 comprise about 50% of known mutations and can be screened for .TMA may also be a consequence of GVHD .When associated with GVHD, patients tend to be steroid refractory/resistant and may have activation of the alternative complement pathway, and thus be amenable to therapy with complement blockade.

- Two consensus guidelines describe clinical criteria for the diagnosis of transplant-associated TMA and include (1) schistocytes on peripheral smear and (2) elevated lactate dehydrogenase .The Blood and Marrow Transplant Clinical Trials Network guidelines also include AKI, unexplained central nervous system dysfunction, and negative Coombs test .Thrombocytopenia, anemia, and decreased haptoglobin are required in International Guidelines from the European Group for Blood and Marrow Transplantation .Unfortunately, these clinical criteria guidelines often do not correlate with histology

Acute GN

- Nephrotic syndrome after transplantation is a rare event (reported incidence of around 1%, with some evidence that this occurrence may be more common with nonmyeloablative therapy) .Typically, this syndrome develops more than 6 months after transplant and is thought to be related to tapering of immunosuppression and chronic GVHD, with dysregulation of both T and B cells and cytokines present as well as a high prevalence of autoantibodies to cellular and surface antigens .Most cases are identified by typical criteria of proteinuria, edema, and hypoalbuminemia. Kidney biopsies may be underperformed in this setting because of thrombocytopenia and coagulation abnormalities that increase the risks of biopsy. The most common pathologies encountered are membranous nephropathy and minimal change disease .In cases of transplant-associated membranous nephropathy, testing for anti-phospholipase A2 receptor antibodies is usually negative .Although the data are limited, most cases of nephrotic syndrome respond to increasing immunosuppression per standard guidelines used to treat these diseases .

Infections

- BK virus and adenovirus infections develop in patients receiving hematopoietic stem cell transplant and may cause AKI. BK virus reactivation within the urogenital system can cause tubulointerstitial nephritis and hemorrhagic cystitis .Adenovirus infection may cause acute tubulointerstitial disease, but more commonly causes cystitis ,especially in patients receiving allogeneic transplant who are heavily immunosuppressed and have severe GVHD

Biomarkers for the Diagnosis of AKI

- Several biomarkers have been widely investigated for early diagnosis of AKI, including neutrophil gelatinase–associated lipocalin (NGAL), urine liver-type fatty acid–binding protein, and others. In the most recent prospective study of Benoit et al. evaluating children undergoing allogeneic transplant, type and severity of AKI was assessed using weekly creatinine, serum cystatin C, and urine NGAL. These biomarkers were combined to define seven subtypes of AKI, depending upon the combination of positive biomarkers. Using this approach, 75% of patients were found to have AKI by at least one measure. Patients with allbiomarker-positive AKI were found to have the highest rates of morbidity and mortality

- The authors concluded that use of all three biomarkers provides a more comprehensive profile of early AKI and identifies patients at highest risk of adverse outcomes, providing opportunities for early intervention .In a study by Deger et al., serum cystatin C, but not urine NGAL, was a useful biomarker for early detection of AKI. By contrast, another study of allogeneic recipients showed significant relationship between urine NGAL and AKI .Shingai et al. reported that higher baseline urine liver-type fatty acid–binding protein was linked with a high risk of AKI in patients receiving allogeneic transplant. There remains a knowledge gap and need for further research

Prevention and Treatment of AKI

General Measures

- Strict control of fluid balance is central to the prevention of post-transplant AKI, and therefore weight, BP, and urine output should be monitored regularly in all patients. Nephrotoxic medications and radiocontrast agents should be used cautiously (and ideally avoided). Other recent developments that may lower risk of AKI include (1) using calcineurin-free regimens for prophylaxis of GVHD, as was shown in a study comparing posttransplant cyclophosphamide with calcineurin-based regimens that demonstrated better kidney function after 1 year in the group receiving cyclophosphamide; and (2) more personalized dosing regimens on the basis of knowledge of patient-specific factors such as drug levels and determining polymorphisms involved in drug metabolism.. As an example, the rate of AKI after total body irradiation and cyclophosphamide conditioning was decreased by 38% when the second dose of cyclophosphamide was guided by measurement of the concentration of its metabolites in plasma after the first dose

- All patients with post-transplant AKI should be evaluated for occult infections, and a urinalysis and a kidney ultrasound should be performed. Nephrotoxic medications should be stopped (if possible), medication dosing should be adjusted according to changes in kidney function, and infections should be treated. Although rare, physicians should consider life-threatening complications such as TMA and hepatic sinusoidal obstruction syndrome. Although there are no established guidelines addressing the role of kidney biopsy after stem cell transplantation, we recommend consideration of biopsy in the following settings:

- (1) AKI of unclear cause, (2) failure of kidney function to recover as expected after initial modifications in therapy, and (3) presence of nephrotic-range proteinuria. As many post-transplant patients are coagulopathic and/or thrombocytopenic, biopsy should be performed with caution. KRT should be started in cases of refractory fluid overload or severe electrolyte disturbances; there is evidence suggesting that continuous convective techniques are preferable in this setting

Specific Treatments for Prevention and Treatment of AKI

Marrow Infusion Syndrome

- Prevention of hemoglobin pigment nephropathy in marrow infusion syndrome includes urinary alkalinization and mannitol-induced diuresis to prevent heme-related nephrotoxicity. Marrow infusion syndrome can be treated successfully with early steroid administration.

Hepatic Sinusoidal Obstruction Syndrome.

- Besides fluid/sodium restriction, administration of albumin together with terlipressin or early treatment with defibrotide, an antithrombotic and fibrinolytic agent, should be considered .Defibrotide prophylaxis (alone or in combination with ursodeoxycholic acid) has been reported to be beneficial in high-risk adult allogeneic transplant recipients, but should be evaluated in randomized trials.

Specific Treatments for Prevention and Treatment of AKI

Acute TMA.

- The most important intervention after diagnosis of TMA is withdrawal of calcineurin inhibitors (.Plasma exchange has not been proven to be effective in randomized trials. Several other interventions, including rituximab, recombinant thrombomodulin, defibrotide, and pravastatin in combination with limaprost, have been reported to be beneficial, but their precise roles remain unclear at this time .The involvement of complement in the pathogenesis of transplant-associated TMA has led to the use of eculizumab with evidence of improved survival
- Of note, the dose needed to achieve complement blockade is higher than in atypical hemolytic uremic syndrome .Other therapies that may show promise include the recombinant C5 inhibitor Ornithodoros moubata complement inhibitor (Coversin) and OMS721, an mAb targeting MASP-2, the effector enzyme of the lectin pathway of the complement system

Table 2. Prevention and management of hematopoietic stem cell transplant-associated AKI

- **Prevention and monitoring**
 - Optimization of fluid balance
 - Careful use of nephrotoxic medication and contrast fluid
 - Monitoring of kidney function
- **Treatment: general measures**
 - Optimization of fluid balance
 - Discontinuation of nephrotoxic medications
 - Aggressive treatment of underlying infections
- **Treatment: specific measures**
 - Marrow infusion syndrome: steroids
 - Hepatic sinusoidal obstruction syndrome: albumin and terlipressin, defibrotide
 - Thrombotic microangiopathy: treatment of hypertension, cessation of CNI, complement inhibition (?)

CKD and Hematopoietic Stem Cell Transplantation

Preexisting CKD

- CKD is a common complication after stem cell transplantation associated with higher morbidity and mortality .On the other hand, presence of CKD is often used as an exclusion criterion when selecting patients to undergo transplant, especially when GVHD prophylaxis with a calcineurin inhibitor is contemplated. Myelodysplastic syndrome, secondary acute myelogenous leukemia, and non-Hodgkin lymphoma are diseases of older patients with higher prevalence of CKD than in younger patients. Kidney function in these patients is frequently worsened by previous chemotherapy and exposure to nephrotoxic drugs. Nonmyeloablative conditioning regimens were developed as less toxic modalities of treatment for elderly patients and those with serious comorbidities, including CKD, who are not eligible for standard myeloablative therapy.

- De Souza et al. reported that mild to moderate decrease in GFR was not associated with worse overall survival, nonrelapse mortality, or treatment-related mortality in 141 patients with high-risk myelodysplastic syndrome or acute myelogenous leukemia receiving reduced-intensity conditioning with fludarabine/melphalan. Kersting and Verdonck showed that, in 13 patients with mildly reduced kidney function before nonmyeloablative allogeneic transplant, more than half of patients had improvement of kidney function after transplantation. It appears that the presence of CKD pretransplant should not be an exclusion criterion in settings where calcineurin inhibitor–free GVHD prophylaxis is available.

CKD after Transplantation

Epidemiology.

- The incidence of kidney failure after hematopoietic stem cell transplantation has been reported to vary between 0% and 60% at ≥ 6 months. This wide variation is likely due, in part, to the use of different definitions of kidney dysfunction, duration of follow-up, and type of transplant. Importantly, stem cell transplant recipients develop ESKD at a rate far higher than seen in the general population, and the incidence of CKD after transplantation is anticipated to rise as the age of patients receiving stem cell transplant continues to increase.

- Hingorani et al. recently assessed a prospective cohort of 434 adults followed from the pretransplant period until a median of 5.3 years post-transplant. The largest decreases in eGFR were identified within the first year after transplantation, with eGFR decreasing from a median of 98 ml/min per 1.73 m² at baseline to 78 ml/min per 1.73 m² by 1 year. As eGFR declined from approximately 60 ml/min per 1.73 m², the hazard of mortality progressively increased relative to a normal eGFR of 90 ml/min per 1.73 m² (1.15 versus eGFR 60 ml/min per 1.73 m² [95% confidence interval, 0.87 to 1.53], 1.68 versus eGFR 50 ml/min per 1.73 m² [95% confidence interval, 1.26 to 2.24], 2.67 versus eGFR 40 ml/min per 1.73 m² [95% confidence interval, 1.99 to 3.60]).

- Investigators noted that, although eGFR remained fairly stable after the initial decline, a decreased eGFR was significantly associated with higher risk of mortality .

- Ando et al. conducted a cross-sectional and retrospective study of 158 patients who survived ≥ 3 years after myeloablative transplantation. By National Kidney Foundation CKD staging, 27 patients (17%) developed CKD stage 3 or greater (stage 3, eight patients [5%]; stage 4, ten patients [6%]; stage 5, nine patients [6%]). Seven patients were started on hemodialysis or received a kidney transplant. Subsequently, Shimoi et al. retrospectively analyzed serum creatinine concentrations for 10 or more years in 77 patients who underwent myeloablative allogeneic transplantation. Cumulative incidence of CKD (defined as a persistent decrease in eGFR below 60 ml/min per 1.73 m²) increased over time, reaching 34% at 10 year

Risk Factors

- . CKD is a long-term complication of stem cell transplantation associated with previous AKI, older age, lower pretreatment GFR, female sex, fludarabine conditioning, GVHD, calcineurin inhibitor exposure, TMA, glomerular diseases (membranous GN, minimal change disease, membranoproliferative GN, FSGS), and a variety of other factors. Radiation therapy has been implicated in post-transplant CKD, possibly by causing subacute or chronic TMA (radiation nephritis). Hypertension has been recognized as a late complication of stem cell transplant, with incidence linked to the development of CKD

- . Albuminuria has been associated with progression of CKD and decreased post-transplant survival. Momoki et al. evaluated 251 patients without preexisting CKD for ≥ 1 year after allogeneic transplantation (median follow-up 4 years). Incident proteinuria ≥ 1 on urine dipstick was found to be a significant risk for incident CKD as defined by a persistent eGFR < 60 ml/min per 1.73 m² (hazard ratio, 4.39; 95% confidence interval, 2.44 to 7.73). The authors concluded that patients who manifest dipstick proteinuria are predisposed to nephropathy and strongly recommended routine monitoring by urine dipstick.

Conclusions

- Hematopoietic stem cell transplantation is a critical therapy for many patients with cancer. AKI occurs commonly after transplant and is associated with significant morbidity and decreased patient survival. Risk of CKD is also higher after hematopoietic stem cell transplantation. Research is ongoing to find reliable biomarkers for the early detection of subclinical kidney injury in the post-transplant setting. Prevention, early recognition, and prompt treatment of kidney injury are essential to improving kidney and patient outcomes.

Thanks for your
attention