The Kidney Effects of Hematopoietic Stem Cell Transplantation

Deirdre Sawinski

Hematopoietic stem cell transplant (HSCT) patients are at risk for acute kidney disease and CKD, which confer excess morbidity and mortality in this patient population. A main cause of acute kidney injury (AKI) in stem cell recipients is prerenal azotemia, but acute tubular necrosis (ATN), obstruction, marrow transfusion toxicity, and hepatic sinusoidal obstruction syndrome also contribute. AKI is an important risk factor for death and CKD among HSCT survivors. CKD is a growing complication of HSCT as more patients are transplanted and survival improves. For most patients, the exact etiology of CKD is never identified, but graft vs host disease and thrombotic microangiopathy are important diagnoses to consider. Stem cell transplant patient survival on dialysis is generally poor, but kidney transplantation is a safe and reasonable option for HSCT recipients who progress to ESRD.

Key Words: Hematopoietic stem cell transplant, Acute kidney injury, Chronic kidney disease, End-stage renal disease, Kidney transplantation

Introduction

Patients receiving hematopoietic stem cell transplants (HSCT) are at risk for acute kidney disease and CKD. Kidney disease confers increased morbidity and mortality in this patient population. The causes of kidney disease are multiple and some are unique to stem cell transplant recipients. This review will discuss the epidemiology and etiologies of acute kidney disease and CKD in HSCT recipients and explore advances in kidney transplantation after HSCT.

Overview of Bone Marrow Transplantation

The number of patients undergoing allogeneic and autologous stem cell transplants in the United States has been steadily increasing since 2001; in particular, there has been a marked increase in the number of unrelated allogeneic transplants performed since the popularization of donor databases and improvements in transplantation techniques. The most common indication for HSCT is lymphoproliferative disorders,[1] which represent more than 60% of all transplants performed yearly. Of these, acute leukemia represents more than half of the allogeneic transplants[1] and 45% of autologous stem cell transplants[1] are performed for multiple myeloma.

The toxicities experienced by patients vary depending on the type of transplant and the conditioning regimen used. In autologous transplants, the patient's own stem cells are collected before the administration of chemotherapy and are later reinfused. In allogeneic transplants, chemotherapy and radiation are administered before the infusion of human leukocyte antigen-matched donor stem cells. The exact conditioning regimen used is specific to the center and depends on the type of transplant planned. Autologous stem cell transplants may receive melphalan alone or in combination with camustine, cyclophosphamide, etoposide, or cytarabine. Allogeneic transplants often use total body irradiation (usually administered in fractionated doses) as part of the conditioning regimen, and concurrent chemotherapy can include cyclophosphamide, etoposide, busulfan or fludarabine. Nonmyeloablative or "reduced-intensity" transplants require lower doses of chemotherapy and radiation and often have fewer side effects. All stem cell transplant patients require prophylaxis against common post-transplant infections. Commonly used medications include antifungals, acyclovir or ganciclovir (for herpes virus and cytomegalovirus), and trimethoprim/sufamethoxazole (for Pneumocystis carnii pneumonia and urinary tract infections). Recipients of allogeneic transplants require calcineurin inhibitors (CNIs) and methotrexate for prevention of graft vs host disease (GVHD); ideally, this is tapered around day +100, but patients who develop chronic GVHD require life-long immunosuppression.

After the myeloablative chemotherapy/radiation is administered and stem cells have been infused, the patient's leukocyte counts will nadir at approximately day +5 to +10. In the neutropenic period between when the patient's counts nadir and before engraftment, there is risk of sepsis. Patients are often febrile and at risk for volume depletion because most develop mucositis and diarrhea. During this time period most patients are treated with intravenous (IV) fluids, often empiric antibiotics and antivirals, and they may have IV contrast imaging studies performed to identify an infectious source. Many of these pre- and peritransplant exposures are

From Renal, Electrolyte, and Hypertension Division, Hospital of the University of Pennsylvania, Philadelphia, PA.

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Address correspondence to Deirdre Sawinski, MD, Renal, Electrolyte, and Hypertension Division, Hospital of the University of Pennsylvania, 3400 Spruce Street, 1 Founders Pavilion, Philadelphia, PA 19104. E-mail: Deirdre.sawinski@uphs.upenn.edu

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nephrotoxic and contribute to a stem cell transplant patient's risk of acute kidney injury (AKI).

AKI

AKI is an extremely common complication of HSCT. The incidence of AKI varies in the literature and depends on the definition of AKI used and the type of stem cell transplant performed. One of the earliest reports by Zager[2] found that 53% of HSCT recipients developed AKI and about half of those necessitated dialysis. In another study, Parikh and colleagues[3] observed near ubiquity of AKI among HSCT recipients. In their cohort of 88 patients who underwent allogeneic HSCT, 92% had at least some decrement in kidney function with a minimum decrease in glomerular filtration rate (GFR) of 25%. More than two thirds of the cohort had a 2-fold increase in serum creatinine or the need for dialysis; severe kidney dysfunction was associated with a greater than 80% risk of death in the series. In a larger, prospective, nested case-control study[4] that defined AKI by doubling of serum creatinine, a 36% incidence of AKI was noted. High rates of AKI in HSCT (30-70%) continue to be observed in more recent studies,[5] and the incidence of AKI requiring dialysis is 1% to 19%.[6] Risk factors for AKI that have been consistent across all studies include hepatic sinusoidal obstruction syndrome (SOS) and the kind of transplant performed. Individual studies[5] have implicated female gender, sepsis, use of amphotericin, lung toxicity, CNIs, intensive care unit (ICU) admission, and acute GVHD as risk factors for AKI, but these have not been a universal finding.[6]

CLINICAL SUMMARY

- AKI is extremely common after stem cell transplant; the most frequently identified etiology is prerenal azotemia.
- CKD occurs in stem cell transplant patients at twice the rate of the general population.
- HSCT patient survival on dialysis is poor.
- Kidney transplant after HSCT is a reasonable option for patients who progress to ESRD.

The risk of AKI is greater in allogeneic transplants than in autologous transplants and greater in myeloablative transplants than in nonmyeloablative transplants. The reported incidence of AKI in allogeneic HSCT is 30% to 70%,[6] compared with rates of 12% to 24% reported in autologous HSCT[6]; the requirement for dialysis was also half as frequent in autologous transplant recipients. A comparison study by Schrier and Parikh[7] noted a frequency of AKI of 21% in autologous transplants, 40% in nonmyeloablative-allogeneic transplants, and 69% in myeloablative-allogeneic transplants performed at their center. Additional data from China[8] described an incidence of 29% within the first 100 days post-transplant in nonmyeloablated recipients. A larger cohort study[9] with an AKI rate of 40.4% confirmed these earlier findings. These superior kidney outcomes are interesting to note because recipients of nonmyeloablative transplants are often older patients with more comorbidities who do not qualify for fully ablative transplants.

AKI in HSCT is associated with poor short- and long-term patient survival. Patients with AKI are at increased risk of death within the first 6 months posttransplant,[3] and overall 1- and 5-year survival is approximately 20% lower for those with AKI than those without.[10] Patients who require ICU transfer or dialysis fare particularly poorly. Observed mortality rates for stem cell transplant patients with AKI in the ICU are greater than 80%[11] and in some case series HSCT patients with AKI requiring dialysis have a mortality rate that approaches 100%.[12] These dismal outcomes underscore the need for AKI prevention and prompt diagnosis whenever possible.

Prerenal azotemia is a frequently encountered etiology of AKI in the HSCT patient (Table 1).[13,14] Nausea, vomiting, and diarrhea are side effects of most chemotherapy regimens, and HSCT recipients often have volume depletion because of these gastrointestinal losses. Mucositis is another major complication of chemotherapy and can result in poor oral fluid intake. During the period of neutropenia that precedes stem cell engraftment, HSCT recipients are at risk for sepsis. The inflammatory cytokine response to sepsis causes arteriolar vasodilation and endothelial injury, resulting in capillary leak syndrome, hypotension, and kidney hypoperfusion and injury.

Acute tubular necrosis (ATN)[5,13,14] is also a common cause of AKI in HSCT patients and can overlap with prerenal azotemia. Patients can develop ATN from hypoperfusion injury or as a result of medications required for transplant. Most of the myeloablative chemotherapy agents are potentially nephrotoxic, especially cytarabine, carmustine, busulfan, and fludarabine.[5] Amphoterecin B and aminoglycoside antibiotics are often administered for neutropenic fever and are well-known causes of ATN.[5] CNIs and methotrexate,[5] used for GVHD prophylaxis and treatment, are also nephrotoxic in high doses and with chronic use.

Urinary tract obstruction should always be considered as an etiology of AKI in the HSCT patient. Antivirals such as acyclovir, when administered intravenously, can precipitate in the urine and form obstructing crystals in the tubules.[15] Volume depletion, rapid infusion of IV acyclovir, and prior CKD all increase the risk of this complication. Patients may also be at risk for extrarenal obstruction because of retroperitoneal fibrosis from radiation, retroperitoneal lymphadenopathy, or clots formed because of hemorrhagic cystitis. Hemorrhagic cystitis