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Acute Kidney Injury in Hematopoietic Cell Transplantation

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Abstract

Hematopoietic cell transplantation (HCT) is becoming an increasingly common treatment modality for a variety of diseases. However, patient survival may be limited by substantial treatment-related toxicities, including acute kidney injury. Acute kidney injury (AKI) can develop in approximately 70% of patients post-transplant and is associated with an increased risk of morbidity and mortality. The development of AKI varies depending on the type of conditioning regimen used and the donor cells infused at the time of transplant and the etiology of is often multifactorial. Epidemiology, risk factors for development, pathogenesis and potential treatment options for AKI in the HCT population will be reviewed as well as newer data on early markers of renal injury. As the indications for and number of transplants performed each year increases, nephrologists and oncologists will have to work together to identify patients who are at risk for AKI to both prevent its development and initiate therapy early to improve outcomes.

Introduction

Hematopoietic cell transplantation (HCT) offers cures for many malignant and nonmalignant hematologic diseases, metabolic disorders, and immune deficiencies that were once incurable or fatal. Worldwide, approximately 30,000–40,000 transplantations are performed annually, and the number continues to increase by 10–20% each year. Despite the improvement in outcomes following HCT, renal injury remains a common complication post-transplant and negatively impacts the outcomes.¹ This review will focus on the epidemiology of acute kidney injury (AKI), risk factors for development, pathophysiology and treatment of AKI in the HCT population.

Acute kidney injury is usually defined as a doubling of baseline serum creatinine within the first 100 days after HCT. However, in the HCT literature AKI is variably defined, thereby making comparisons among studies difficult. Consequently, the incidence of AKI after HCT ranges between 21–73%.^{1–13} The severity of AKI in the HCT population is commonly defined by grades. Grade 1 is the least severe, characterized by a less than two-fold rise in serum creatinine with a decrease in creatinine clearance of >25%. Grade 2 refers to more than a doubling of serum creatinine without the need for dialysis, and grade 3 refers to AKI requiring dialysis. This review will focus primarily on Grades 2 and 3 AKI. These definitions are contingent upon baseline serum creatinine as pre-transplant renal dysfunction has been shown to impact outcomes.¹⁴ Therefore, careful assessments of serum creatinine,

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urinalyses and more formal estimations of glomerular filtration rate are warranted during pre-HCT evaluation.

Current Methods of HCT

Source of infused hematopoietic cells

There are various types of HCTs performed today each with varying risks and toxicities, including renal injury. Autologous transplants involve the harvesting of a patient's own bone marrow or peripheral blood hematopoietic cells prior to high dose myeloablative therapy, followed by re-infusion. Allogeneic transplants use bone marrow or peripheral blood hematopoietic cells from family members (ideally, HLA-matched siblings) or HLA-matched unrelated donors or hematopoietic cells from umbilical cord blood. Syngeneic transplants are from an identical twin donor. In allogeneic HCT, the infusion of donor hematopoietic cells is preceded by either myeloablative therapy (usually a combination of chemotherapy drugs or chemotherapy plus total body irradiation (TBI)) or reduced-intensity allogeneic (but immunosuppressive) therapy that allows host hematopoietic cells to co-exist with donor cells (mixed hematopoietic cell chimerism). The distinguishing feature between myeloablative and reduced-intensity allogeneic transplantations is the conditioning regimen. The goal of myeloablative regimens is to kill all residual cancer cells (autologous or allogeneic transplantation) and in allogeneic HCT, to cause immunosuppression that allows donor cell engraftment. Myeloablative transplantation involves significant toxicities, and therefore is only offered to younger and healthier patients. The goal of reduced-intensity regimens is to provide immunosuppression in order to allow engraftment of the transplanted donor cells and relies on a graft-versus-tumor effect to kill tumor cells. The reduced-intensity regimens are less toxic and therefore can be used in older patients, or patients with substantial co-morbidities. The most common myeloablative regimens are cyclophosphamide plus TBI; busulfan plus cyclophosphamide; busulfan plus fludarabine; and BEAU. Reduced-intensity regimens contain lower doses of chemotherapy, for example, fludarabine plus 2–4 cGy TBI along with intense posttransplant immune suppression.¹⁵

Prophylaxis for complications

Allogeneic graft recipients received prophylaxis against acute graft vs. host disease (GVHD) with immunosuppressive drugs, usually cyclosporine or tacrolimus plus pulsed doses of methotrexate; mycophenolate mofetil and sirolimus are also used.¹⁶ Prophylactic drugs against graft vs. host disease typically continue to day +80 post-transplant after myeloablative conditioning regimens, but are usually tapered earlier than this after reduced-intensity conditioning to promote a graft vs. tumor effect. Prophylaxis for infection usually includes acyclovir, trimethoprim/sulfamethoxazole to prevent *Pneumocystis jirovecii* infection, oral fluconazole for prophylaxis of candidal infection, and pre-emptive ganciclovir or foscarnet for cytomegalovirus disease among viremic patients.^{17–19}

Treatment of GVHD

Patients who develop acute GVHD (~60% of allograft recipients) are treated with high-dose prednisone (1–2 mg/kg/day), often for weeks to months, depending on the clinical response. Patients who fail to respond to prednisone therapy are treated with more intensive immunosuppressive drugs and biological agents including anti-T-cell antibodies such as anti-thymocyte globulin, or Campath, anti-TNF- α biologic agents, and additional drugs such as sirolimus or mycophenolate mofetil. Some patients receive extracorporeal photopheresis or phototherapy with direct exposure to UVA. Such intense immunosuppression is frequently attended by viral, bacterial and fungal infections, including organisms that can specifically infect the kidney such as adenovirus and JC/BK polyoma virus. Allograft recipients are at risk for the development of chronic GVHD, a multi-organ immunologic

disorder that often requires prolonged treatment with calcineurin inhibitors and other immunosuppressive drugs. However, in about half of allograft recipients, tolerance develops, allowing the eventual discontinuation of immunosuppressive drugs and recovery of immunity within 5 years. Ten percent require treatment for greater than 5 years and 40% die without resolution of their chronic GVHD.²⁰

Epidemiology of AKI

Myeloablative Conditioning Regimens and Allogeneic HCT

In this population, AKI usually occurs within the first 2 to 4 weeks post-transplant.^{2, 9} Recent data suggests that up to 70% of patients undergoing myeloablative HCT develop AKI.^{1, 2, 4, 8, 21} Multiple retrospective studies have reviewed the incidence of AKI in this population (Table 1). Two retrospective reviews, one of 88 patients at the University of Colorado and the other of 140 patients at the Hospital de Santa Maria in Lisboa, Portugal found an incidence of AKI of 69% and 30% respectively.^{6, 8} The incidence of severe AKI requiring dialysis varies from 1–19%.^{1, 4, 6, 8, 13, 21, 22} In a prospective study of 147 patients receiving an allogeneic transplant at the Fred Hutchinson Cancer Research Center, risk factors for the development of AKI included amphotericin use (either liposomal or conventional) and hepatic sinusoidal obstruction syndrome(SOS), formerly known as hepatic veno-occlusive disease. Additionally, the risk of AKI was decreased 30% for every 0.1 mg/dL increase in baseline serum creatinine.² It is conceivable that this association is in part an artifact of the definition chosen in this study as the absolute change required to meet a doubling of baseline serum creatinine would be less for a person with a low baseline level than a higher one. However, a possible basis for the reduced risk of AKI associated with a higher baseline serum creatinine is supported by experimental animal data demonstrating increased cholesterol in renal tubular cells at times of systemic stress or direct tubular injury.^{23, 24} Increased levels of cholesterol in renal tubular cells may confer a “cytoresistant” state protecting the kidney from further injury. This cytoresistant state can persist for a variable length of time after the initial injury.²³ Thus, if the higher baseline serum creatinine reflects earlier injury, patients with such levels may truly be at a lower risk of AKI. A recent study of 363 patients undergoing allogeneic transplant determined that hypertension at the time of transplant as well as admission to the ICU were associated with an increased risk of AKI.¹ The following risk factors have variably been associated with AKI: female gender, high risk malignancy, acute graft vs. host disease, lung toxicity and donor type (related vs. unrelated).^{2, 4, 8, 13}

Myeloablative Conditioning Regimens and Autologous HCT

The incidence of AKI following myeloablative regimens and autologous HCT ranges from 12–32% with 3–16% of patients with AKI requiring dialysis.^{6, 10, 12, 25} In a retrospective review of 232 patients with breast cancer who received an autologous transplant, AKI grade 2/3 developed in 21% of patients and 3% required dialysis. Risk factors for development of AKI in this cohort of patients included hepatic toxicity (including SOS), lung toxicity and sepsis.¹⁰ A study of AL amyloidosis patients treated with autologous HCT found a similar incidence of AKI and dialysis, 21% and 5% respectively. In this study, baseline risk factors for AKI included decreased creatinine clearance, proteinuria and cardiac involvement. In addition, post transplant risk factors included melphalan use and bacteremia.²⁵

Comparison of AKI after myeloablative conditioning regimens: effect of autologous vs. allogeneic HCT

The incidence of AKI in autologous HCT is lower than that seen in allogeneic HCT. A single center, retrospective study at the Hospital de Santa Maria in Lisboa, Portugal reviewed 140 patients who underwent autologous or allogeneic HCT following myeloablative regimens,

and found that the incidence of AKI in recipients of allogeneic HCT was 27% compared to an incidence of 12% in those undergoing autologous HCT. They also found that the patients who received allogeneic HCT were more likely to need dialysis than the recipients of autologous HCT (33% vs. 16%).⁶

In a prospective study in the Bone Marrow Transplantation Unit of Istanbul School of Medicine, 47 consecutive patients undergoing autologous or allogeneic HCT were followed. The incidence of grade 2–3 AKI was 46% in the allogeneic group compared to 24% in the autologous group. In contrast to the previously described study above, the difference in incidence of AKI in this study was statistically significant. There was no difference in baseline age, serum creatinine and creatinine clearance between the groups. Baseline serum albumin levels (<3.5 mg/dl) were associated with an increased risk of AKI in both autologous and allogeneic transplant recipients. Different risk factors for AKI were identified in the two groups: sepsis in the autologous HCT recipients and SOS and cyclosporine toxicity in the allogeneic HCT recipients.¹² Overall, the data suggests that autologous HCT is associated with less severe injury to the kidney when compared with allogeneic HCT. The absence of exposure to calcineurin inhibitors and of acute GVHD may explain the lower incidence of AKI after autologous HCT compared to allogeneic HCT. In addition, because the use of conditioning regimens that contain hepatic sinusoidal toxins is more common in allogeneic transplant recipients, there is a higher frequency of hepatic SOS, the primary risk factor for AKI after HCT.

Reduced-Intensity Conditioning Regimens and Allogeneic HCT

The incidence of AKI in this population is consistently lower than the incidence in studies involving myeloablative regimens despite these patients being older, having more comorbidities and a higher incidence of CKD at baseline, that is between 33–47%.^{3, 4, 9, 26} The percentage of patients requiring dialysis ranges from 0–4%.^{3, 4, 9, 26} Unlike those undergoing myeloablative HCT, AKI in reduced-intensity transplant patients is not usually isolated to the first 2 to 3 weeks after transplant, but occurs at any point in the first 3 months.⁹ Risk factors in this patient population include administration of methotrexate, more than three rounds of chemotherapy prior to the transplantation, GVHD grades III–IV,^{3, 26} the occurrence of hepatic SOS, and requirement for artificial ventilation and a lower baseline serum creatinine.³ Diabetes mellitus is not consistently associated with AKI.^{3, 26} Cyclosporine levels have not been shown to be associated with an increased risk of AKI.³ In studies that compare myeloablative regimens to reduced-intensity regimens, the overwhelming risk factor associated with development of AKI is the use of a myeloablative conditioning regimen, with a 4.8 fold greater incidence of AKI.⁴

Potential Etiologies of Acute Kidney Injury in HCT

Tumor lysis

Tumor lysis syndrome is a rare cause of acute kidney injury in patients after HCT, seen more commonly in patients with residual disease or an underlying lymphoproliferative disorder at time of HCT. Cases of tumor lysis syndrome have been reported in patients after TBI used during conditioning and after reduced-intensity regimens.^{27, 28} Additionally, post-transplant complications such as SOS and acute GVHD may lead to hyperuricemia.²⁸ The renal injury is related to tubular obstruction and dysfunction secondary to hyperuricemia and hyperphosphatemia. Hyperuricemia has also been associated with renal vasoconstriction and production of pro-oxidative and pro-inflammatory mediators which may contribute to ongoing vascular and tubular injury.²⁹ Tumor lysis syndrome is relatively uncommon in the HCT population as most patients are in remission at the time of transplant.

Sepsis

Sepsis leads to a combination of insults, both hemodynamic and inflammatory, that coalesce to cause renal failure. In sepsis, there is an initial inflammatory response leading to systemic arteriolar vasodilation and endothelial injury. The resultant capillary leak that occurs leads to renal hypoperfusion. In addition, early after sepsis there is a constriction of the renal vessels further decreasing renal perfusion. Injury to the tubules themselves causes a local release of cytokines and chemokines that cause local inflammation and further intrarenal injury.³⁰ In addition, the antimicrobials commonly used to treat sepsis are often nephrotoxic.

Nephrotoxic Medications

Amphotericin B is directly toxic to the distal tubular epithelium. It also induces renal vasoconstriction reducing renal blood flow and glomerular filtration rate (GFR). Studies have demonstrated an increased occurrence of AKI in patients receiving either conventional or liposomal preparations of amphotericin.² Several newer, antifungal agents with less nephrotoxicity are currently available, and therefore the use of amphotericin B should be limited whenever possible to documented fungal infections with susceptible organisms only.

Aminoglycosides are also used in HCT patients, both empirically and therapeutically. Although evidence does not identify aminoglycosides as a risk factor for AKI in HCT recipients, they likely contribute to its development, especially when used in the setting of pre-existing kidney dysfunction, co-administered with other nephrotoxic medications and/or used in the setting of sepsis. The nephrotoxicity of aminoglycosides is related to the intracellular accumulation of the drug resulting in disruption of membrane permeability and inhibition of intracellular phospholipases in proximal tubular cells. The progressive loss of proximal tubular function may be reduced by administering aminoglycosides less frequently. In a randomized, controlled trial of once daily vs. multiple daily dosing of tobramycin in 54 ICU patients, a marked decrease in enzymuria as measured by urinary N-acetyl β -D glucosaminidase and alanine aminopeptidase, was found in those patients who received once daily tobramycin. The authors postulate that the decrease in enzymuria reflects a decrease in renal tubular damage and suggest that once daily dosing may be the preferred method of dosing in critically ill patients.³¹ The theory behind once daily dosing is that despite exposure to a higher peak concentration of medication, there is a prolonged period of little or no drug exposure which may reduce the incidence of nephrotoxicity.

Calcineurin inhibitors are commonly used in allogeneic transplant recipients for the prevention and treatment of GVHD. They have known nephrotoxic effects, most commonly secondary to their potent vasoconstricting properties and ability to cause endothelial injury. Despite this, the majority of studies fail to show a significant association between cyclosporine blood levels and development of AKI.⁸ A large, retrospective study of 272 patients undergoing myeloablative allogeneic transplant revealed no association between the use of calcineurin inhibitors and the development of AKI.⁵ Another study of 363 recipients of allogeneic myeloablative HCT failed to show an association between mean cyclosporine trough levels and serum creatinine.¹³ Multiple studies have compared the use of tacrolimus versus cyclosporine and have found that there is no difference in the incidence of AKI between these two agents.^{9, 32}

Hepatic Sinusoidal Obstruction Syndrome

Hepatic sinusoidal obstruction syndrome (SOS), formerly known as hepatic veno-occlusive disease, causes acute portal hypertension that occurs as a result of acute radio-chemotherapy-induced injury to sinusoidal endothelial cells. SOS is one of the most frequently encountered and serious complications in the HCT population, occurring in up to 60% of patients who receive very high, cyclophosphamide-based myeloablative,

conditioning therapy. There is a well-known association between this entity and acute kidney injury. SOS begins as a fluid-retentive state with low urinary sodium that leads to peripheral edema and weight gain within the first few days after transplantation. Common signs and symptoms include hepatomegaly, right upper quadrant pain, ascites, elevated serum aminotransferases and serum bilirubin levels. These features occur prior to the development of renal insufficiency. Weight gain has also been shown to be highly correlated with SOS, and may serve as a marker of impending renal injury.² The portal hypertension that results from hepatic sinusoidal injury may lead to decreased renal perfusion and tubular injury (Figure 1).^{2, 33, 34} Risk factors for the development of SOS include underlying necro-inflammatory and fibrotic liver diseases and the use of agents toxic to sinusoidal endothelial cells (i.e. cyclophosphamide and TBI 12 Gy).³⁵ Treatment for SOS with recombinant human tissue plasminogen activator and defibrotide have a response rate of approximately 45%.³⁶

Hematopoietic cell transplantation-associated thrombotic microangiopathy

Thrombotic microangiopathies (TMA) encompass a spectrum of diseases from thrombotic thrombocytopenic purpura (TTP) to hemolytic uremic syndrome (HUS). These entities usually occur between 20 and 99 days post-transplantation, with TTP occurring earlier after transplant. The incidence ranges from 0–74%.¹⁷ The diagnosis, based on hemolytic anemia, thrombocytopenia, neurologic impairment and renal dysfunction, can be difficult in HCT patients. Assessment of the peripheral smear for schistocytes, can aid in early diagnosis. The etiology in HCT-related TTP cases is different than the general population in that HCT-related TMA is not due to deficiencies or abnormalities in von-Willebrand factor-cleaving protease, but instead from direct endothelial injury from calcineurin inhibitors, high dose chemotherapy, total body irradiation, and acute GVHD.^{37–40} This difference may account for the failure of plasmapheresis to provide benefit for TTP in the HCT population. For patients with HCT-related TMA, the treatment should be based on the underlying mechanism, i.e. discontinuation of the calcineurin inhibitor, or in the case of GVHD-related TMA, continued treatment of the acute GVHD or directing therapy to mitigate endothelial injury.^{41–43}

Albuminuria and Proteinuria

In a prospective study of 142 patients undergoing HCT, the prevalence of albuminuria and proteinuria at day 100 was 64% and 15% respectively.⁴⁴ Albuminuria was associated with acute graft vs. host disease (aGVHD) and bacteremia but not AKI. Presence of albuminuria at day 100 was associated with a four-fold increased risk of developing chronic kidney disease at 1 year post-transplant, defined as a GFR <60 mL/min/1.73m². Non-relapse mortality at 1 year was increased approximately 7-fold in patients with proteinuria at day 100 and overall survival was decreased compared to patients without proteinuria at day 100 post-transplant (Figure 2). We have speculated that inflammatory damage to the tubules from GVHD leads to albuminuria, and that albuminuria may be a subclinical marker of GVHD that can be detected before the disease clinically manifests in the gut, skin, and liver (Figure 3). Alternatively, the renal vasculature, glomerulus, and perhaps the proximal tubular cells are affected by the GVHD process, making the kidney another target organ in acute GVHD. The presence of albuminuria and proteinuria early after transplant suggests that subclinical renal injury occurs which may not be reflected by changes in serum creatinine and that even minor damage to the kidney can impact long-term outcomes and mortality.

Management of AKI

Acute kidney injury following HCT is associated with higher one-year mortality and chronic kidney disease, and thus preventing its occurrence is paramount to improving outcomes after HCT. Avoidance of myeloablative conditioning regimens in patients at increased risk for AKI would reduce the likelihood of AKI. Avoidance of nephrotoxic agents, especially amphotericin, in favor of newer antifungal medications that do not have an effect on the kidney may also reduce the incidence of AKI. When known nephrotoxic agents are used, close monitoring of drug levels and adjustment of dosing regimen will further reduce insults to kidney function. Lastly, because of the strong association between SOS and AKI, prevention of SOS and portal hypertension would reduce the incidence of AKI. Alterations in conditioning regimens at the Fred Hutchinson Cancer Research Center have led to a significant decrease in the frequency of SOS and subsequently a decrease in the frequency of AKI (McDonald GB, personal communication).

In the majority of cases, the management of AKI is supportive. Studies comparing intermittent hemodialysis versus continuous renal replacement therapy in patients admitted to the intensive care unit are equivocal (reviewed in⁴⁵). Given that once dialysis is indicated, the mortality is greater than 80% regardless of transplant type, measures to decrease the frequency and severity of AKI are needed to decrease the morbidity and mortality associated with an otherwise life-saving therapy. Nephrologists should be involved early in the management of these patients to assist with fluid balance and blood pressure control, medication dosing and evaluation of even small increases in serum creatinine.

Outcomes

Mortality rates have been shown to be higher in patients who undergo at least a 50% reduction in GFR when compared to patients who do not suffer AKI regardless of the type of transplant performed. Six month mortality rates have been reported to be as high as 65.5% in allogeneic recipients with AKI.⁸ Multiple studies have demonstrated that mortality rates increase as the severity of AKI increases.^{3, 4, 7, 9, 26, 46} Mortality rates for patients requiring dialysis are 80%–100%, regardless of the conditioning regimen used.^{9, 10, 21} One year non-relapse mortality rate for myeloablative HCT recipients who develop AKI is 32% versus 19% in the reduced-intensity regimen group with AKI.⁴ Other studies have shown 1 year mortality rates in reduced-intensity regimen HCT to be as high as 42%–47% in those developing AKI, compared to 26%–28.5% in those without AKI.^{9, 26} The development of AKI early after transplant in reduced-intensity regimens also negatively impacts 5-year overall cumulative survival, with 41.6% of patients who developed AKI surviving compared to 67.1% of patients without AKI alive at 5 years post-transplant.⁷

There is varying data on the impact of AKI on long term kidney prognosis. For most patients who survive three months post HCT, creatinine clearance improves from initial AKI insult. A retrospective analysis of 358 patients who underwent reduced-intensity HCT demonstrated that only 13% of patients who suffered AKI had persistently elevated creatinine levels after the acute event; the remaining AKI patients' creatinine levels returned to within or lower than 1.5 times of baseline. Those patients whose elevated creatinine levels persisted did not have a higher risk of mortality when compared to those whose creatinine levels improved. This suggests that it is the AKI event itself that affects overall mortality rather than the final creatinine value.⁴⁷ Even minor changes in serum creatinine (grade 1 AKI) are associated with an increase risk of non-relapse mortality at 1 year and a decreased overall survival.⁷ In one recent study of allogeneic transplant recipients, significant co-morbid complications in addition to development of AKI seem to be the major predictors of death.¹ Survival rates in patients who developed AKI in the absence of other co-morbid

conditions were not different from those patients who did not develop AKI.¹ However, in a meta-analysis of patients with AKI after HCT, AKI was an independent predictor of mortality in patients with Grade 3 AKI after myeloablative allogeneic HCT suggesting that patients are dying because of their AKI and not simply with AKI (Figure 4).⁴⁶ After adjusting for age, history of cardiovascular disease, high risk disease and chronic GVHD, AKI was found to be an independent predictor of both 5-year all cause mortality and 5-year non-relapse mortality in patients receiving reduced-intensity regimens.⁷ AKI is also a risk factor for later development of CKD in these patients.

Conclusions

AKI is associated with an increase in morbidity and mortality in the HCT population. The incidence of AKI varies based on the type of transplant with the highest frequency of AKI found following myeloablative conditioning regimens and allogeneic transplant compared to autologous and reduced-intensity and allogeneic transplant recipients. In all three transplant types, mortality is clearly increased with AKI, with a greater risk of mortality in those patients requiring dialysis. Consequently, early recognition of patients at risk for development of AKI post-transplant and prevention of the occurrence of AKI is paramount to improve the outcomes of an otherwise life-saving therapy. The management of these patients needs to involve both the nephrologist and the oncologist prior to transplant to identify patients at risk for AKI and early after transplant when only minor changes of serum creatinine are present and interventions such as adjustment of drug dosing and serum levels, use of newer antifungal agents and early intervention with renal replacement therapy may be beneficial. Recognition that the kidney may be a target organ of GVHD and evaluating for the presence of albuminuria and/or proteinuria early after transplant may also guide therapy and reduce the burden of kidney disease in this patient population.

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Figure 1. Acute Tubular Necrosis. Most tubules show epithelial damage including loss of brush border, cytoplasmic decapitation and cell drop-off. Residual lining cells have increased N:C ratios or attenuated cytoplasm; a rare mitotic figure is evident (arrow). Cytoplasmic vacuolization is focal (*). (Hematoxylin & Eosin; 200X)

Figure 2. Kaplan-Meier curves of albuminuria and overall survival from day 100 to 1 year post-HCT. N=44 for ACR<30; N=58 for ACR 30–300; N=18 for ACR ≥ 300. Reproduced with permission from⁴⁴

Figure 3. Renal biopsy from a patient with nephrotic-range proteinuria post-HCT. A moderately intense mononuclear cell infiltrate is within the interstitium and focally prominent within some tubules where it is associated with epithelial damage. Reactive, degenerative and regenerative epithelial changes are noted. (Jones Methenamine Silver; 400X).

Figure 4. Kaplan-Meier survival graph demonstrating a significant association of the 3 grades of grades AKI with 6-month mortality in patients after hematopoietic cell transplant. Reproduced with permission from⁴⁶

Table 1

Summary of Literature of AKI after HCT.

Type of conditioning regimen/source of donor cells*	No of patients	Incidence of AKI (%)**	Risk Factors	Median Onset	Non-Relapse Mortality at 1 yr	Year ^{Ref}
Myeloablative	363	49.6	HTN at time of HCT, admission to ICU	40	18(at 6 months)	2007 ¹
Myeloablative	147	36	Amphotericin, SOS, lower baseline Cr	33	ND	2005 ²
Myeloablative	97	81	GVHD III-IV, SOS		ND	2003 ¹³
Myeloablative	88	69	Lung toxicity, VOD associations	16	ND	2002 ⁸
Myeloablative/Autologous	232	21	Liver and lung toxicity(incl SOS), sepsis(associations)	28	ND	1996 ¹⁰
Myeloablative/Autologous	173	21	ND	7	ND	2003 ²⁵
Myeloablative/Allo/Auto	22/25	68/32	ND	51/37	ND	2006 ¹²
Myeloablative/Allo/Auto	90/50	27/12	ND	ND	ND	2006 ⁶
Myeloablative/Allo/Auto	242/30	54/39	Weight gain, hyperbilirubinemia, amphotericin B use, sepsis, serum creatinine >0.7 mg/dl pre-txplant	14	ND	1989 ⁵
Myeloablative /RIC	140/129	73/47	Myeloablation	26/26	32/19	2005 ⁴
RIC/Allogeneic	188	44	MTX, DM, GVHD III-IV, more than 3 previous chemo treatments	31	33	2009 ²⁶
RIC/Allogeneic	82	53.6	ND	37.3	18	2008 ⁷
RIC/Allogeneic	358	56	ND	ND	ND	2008 ⁴⁷
RIC/Allogeneic	150	42	Absence of vascular disease, lower baseline creatinine, acute GVHD, CMV reactivation	ND	ND	2007 ³
RIC/Allogeneic	253	40.4	ventilator use, GVHD, product source (marrow vs. peripheral blood)	60	ND	2004 ⁹

* Allo: Allogeneic HCT; Auto: Autologous HCT; RIC: Reduced-intensity conditioning HCT

** AKI refers to AKI stage 2 and 3

Ref, Reference

ND, Not determined in the paper