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Renal Complications of Hematopoietic Stem Cell Transplantation

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Hematopoietic stem cell transplantation (HSCT) offers curative potential in the treatment of both malignant and nonmalignant disorders of lymphohematopoiesis. Over the last two decades, advances in graft matching, expanded donor registries, better post-graft immunosuppression, and improved management of infectious complications have fueled dramatic growth in these transplants. Despite this progress, renal complications of HSCT remain a very important cause of morbidity and mortality. Peri-transplant acute renal failure (ARF) is common and costly, and ARF requiring dialysis is associated with extraordinarily high mortality. The cause of ARF is usually multifactorial, including nephrotoxic drugs, sepsis, and hepato-renal syndrome from veno-occlusive disease. The risk of ARF also depends on the type of conditioning (myeloablative or non-myeloablative) and the source of stem cells (autologous or allogeneic). HSCT-associated nephrotic syndrome is increasingly recognized as a distinct clinical entity. Chronic kidney disease (CKD) occurs in at least 20% of long-term graft survivors and is most often caused by a thrombotic microangiopathy (TMA) syndrome or chronic calcineurin inhibitor (CNI) toxicity. This issue of *Nephrology Rounds* updates marrow transplant techniques, describes renal toxicities, and outlines the diagnostic approach and management of these complications.

The observation in 1951 that mice could be protected from otherwise lethal doses of irradiation by shielding their spleens with lead set the stage for the discovery of transplantable hematopoietic stem cells and ushered in the era of bone marrow transplantation.[1] The first human bone marrow transplants were undertaken in the late 1950s and, similar to early kidney transplants, met with little success. It was not until the 1980s that HSCT was performed on significant numbers of patients after large trials showed that several leukemias could be cured as long as transplant was undertaken early in the course of the disease. Since then, HSCT has grown dramatically. It is now considered primary therapy for a number of malignancies and a wide variety of primary immonodeficiencies and metabolic diseases. There were 17,700 HSCTs performed in the United States in 2002, with large increases over the last 10 years in particular (Figure 1A). A recent factor driving the growth of HSCT has been the development of non-myeloablative protocols. These regimens employ reduced-intensity conditioning with correspondingly less organ toxicity, opening the way for older patients and those with comorbidities to be transplanted (Figure 1B).

Overview of HSCT protocols

The general strategy for HSCT has three components.

- First, intensive conditioning is administered, consisting of irradiation and/or chemotherapy for the purpose of immunoablation and disease eradication.
- Second, donor hematopoietic cells are infused to rescue the patient from myeloablation.
- Third, post-graft immunosuppression is given to control graft-*versus*-host disease (GVHD) and to establish graft-host tolerance.

Myeloablative conditioning regimens employ otherwise lethal doses of irradiation and chemotherapy. Not surprisingly, these protocols are associated with significant morbidity, including renal failure, and for this reason myeloablative HSCT has traditionally been limited to younger patients without comorbidities. Non-myeloablative allogeneic transplants are a more recent development utilizing reduced-intensity conditioning designed to allow

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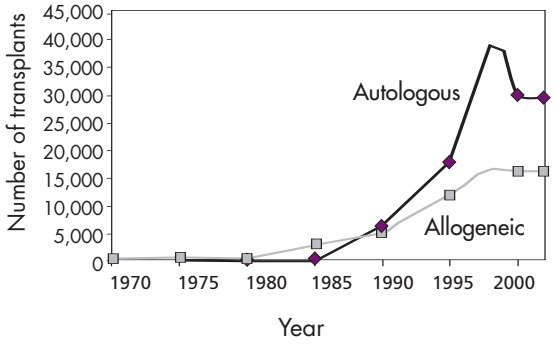
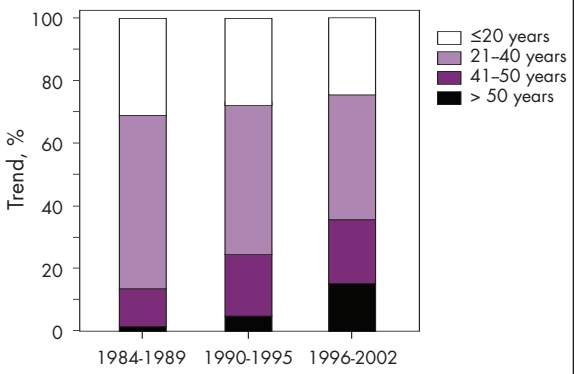
Figure 1A: The overall number of HSCTs performed worldwide has increased dramatically over the last 15 years



Adapted with permission from the International Bone Marrow Transplant Registry.

Figure 1B: Age at time of HSCT for leukemias has steadily risen over the last 2 decades



engraftment of donor stem cells without myeloablation. At least initially, the result is mixed chimerism of donor and host stem cells. These so-called "mini-allo" transplants take advantage of the graft-*versus*-tumor effect seen in many of the more indolent cancers such as chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL).

The source of hematopoietic stem cells is from either a donor (allogeneic) or from the patient (autologous). Allogeneic cells are harvested from marrow, peripheral blood, or cord blood. The establishment of large registries for bone marrow donors and typed cord blood has greatly increased the chance of finding a match in allogeneic transplants. In autologous HSCT, cells are harvested from either the marrow or peripheral blood of the patient to be transplanted, then stored frozen in a cryopreservative (dimethyl-sulfoxide or DMSO) for infusion after conditioning.

The decision to perform an allogeneic or autologous HSCT depends on several factors, including the availability of a matched donor and issues related to the underlying disease such as the immunologic sensitivity of the tumor (ie, its susceptibility to the graft *versus* tumor effect), whether or not tumor cells are present in the patient's marrow or circulation, and the susceptibility of the tumor cells to high-dose chemotherapy. Indolent cancers like CML can be effectively controlled by the graft *versus* tumor effect in allogeneic HSCT, for example. Aggressive lymphoproliferative disorders like Hodgkin's disease are more susceptible to high-dose chemoradiotherapy, but require autologous HSCT for reconstitution of the immune system after therapy. Frequently, patients may undergo initial autologous HSCT and subsequent allogeneic HSCT after relapse.

The third component of HSCT consists of immunosuppression given to promote tolerance of the graft and reduce GVHD. Standard regimens include regular cyclosporine or methotrexate, given for the first 3 months post-transplant. These regimens are associated with a 25% incidence of moderate to severe acute GVHD. While many transplant recipients are on CNIs for a relatively short time, roughly 50% of HSCT survivors develop chronic GVHD and are maintained on calcineurin for years with attendant risks of nephrotoxicity.[2]

Incidence of ARF after HSCT

The risk of ARF after HSCT varies according to the type of transplant (Table 1). In myeloablative allogeneic HSCT, Zager originally reported that 53% of patients developed ARF (defined as >50% reduction in glomerular filtration rate [GFR]), with half of these patients requiring dialysis.[3] These early observations hold true today. In several more recent analyses, the overall incidence of ARF in myeloablative HSCT is between 36% and 78%, with 21% to 33% of these patients requiring dialysis.[4] In a recent meta-analysis comprising 1,211 HSCT recipients, ARF was independently associated with a >2-fold increased risk of death.[5] The mortality associated with ARF requiring dialysis is >80%, at least in part because of concurrent multi-organ failure[6,7] These studies were performed before the replacement of amphotericin B and the aminoglycosides with less toxic alternatives (caspofungin or voriconazole and fourth generation cephalosporins, respectively) for the routine treatment of fever and neutropenia.[8] It is likely that these changes have reduced the overall incidence of HSCT-associated ARF, but this has not yet been studied.

The incidence of ARF after autologous HSCT is lower than after allogeneic HSCT, ranging from between 15%-21% in recent studies.[9,10] Two factors likely explain the lower incidence of ARF in autologous HSCT. First, GVHD does not occur in autologous HSCT and, therefore, nephrotoxic CNIs are not required. Second, most autologous HSCTs are performed with peripheral blood stem cells; these engraft sooner than marrow- or cord-derived stem cells, shortening the cytopenic interval, and reducing the risk of bleeding, sepsis, and nephrotoxic antibiotic exposure.

Fewer studies have examined the incidence of ARF after non-myeloablative allogeneic HSCT, but existing

Table 1: Rates of ARF according to type of hematopoietic cell transplant[4]

HCT type	Mod-severe ARF[a]	ARF requiring RRT[b]	Mortality if RRT
Myeloablative			
– Allogeneic	30%-60%	20%-30%	80%
– Autologous	15%-20%	5%-10%	80%
Non-myeloablative	40%	3%-5%	>70%

[a] Moderate to severe ARF is defined as at least a doubling of the serum creatinine whether or not renal replacement therapy was required.
[b] RRT, renal replacement therapy

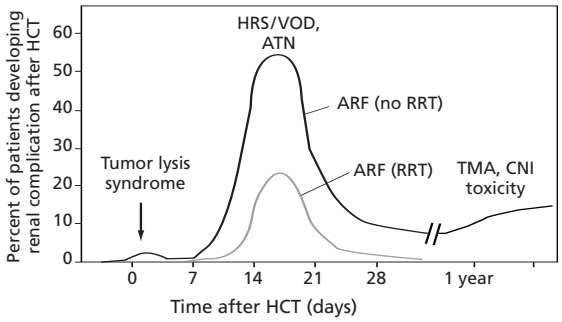
data indicate that the incidence is lower than after myeloablative HSCT. In a recent study, Parikh et al found a cumulative incidence of ARF (defined as doubling of serum creatinine [SCr] at 4 months) in non-myeloablative HSCT of 40.4%, but only 4.4% of all patients required dialysis.[11] Most cases of ARF were reversible with a lower CNI dose. In distinction with myeloablative HSCT, veno-occlusive disease was not a major cause of ARF. The timing of ARF in non-myeloablative HSCT was distributed over the first 3 months post-HSCT; whereas, in myeloablative HSCT, ARF occurs primarily in the first 3 weeks. Similar to myeloablative HSCT, non-myeloablative recipients that develop ARF requiring dialysis have >70% mortality.

Types of ARF after HSCT

The etiology of HSCT-associated ARF can be categorized according to the time period after transplantation (Figure 2).[12,13] In the first days following the transplant, patients are mainly at risk for tumor lysis syndrome. Tumor lysis prophylaxis, including allopurinol and volume expansion for patients at risk (those with aggressive cancers or bulky tumors at transplant), have made this an uncommon complication of chemoradiotherapeutic conditioning. Historically, marrow infusion toxicity also presented in this early time period. This syndrome consisted of ARF following autologous marrow infusion resulting from pigment nephropathy, due to hemolysis of contaminating red blood cells during stem cell storage, or from osmotic nephrosis due to infusion of large volumes of cryopreservative/DMSO.[14,15] This syndrome has been eliminated with the use of lower DMSO concentrations and divided infusions of unusually large stem cell preparations.

During the first few weeks after conditioning patients are at highest risk for ARF.[13] A pre-renal state is common resulting from vomiting and diarrhea, the consequence of conditioning, acute GVHD, or CNIs. Exposure to potentially nephrotoxic agents, including methotrexate, amphotericin B, acyclovir, aminoglycosides, angiotensin-converting enzyme (ACE) inhibitors, intravenous contrast, and CNIs predisposes the patient to the development of acute tubular necrosis. Thrombocytopenia and neutropenia predispose to hemorrhagic or septic shock, respectively, and may lead to acute tubular necrosis. Obstructive uropathy develops in the setting of severe hemorrhagic cystitis (from cyclophosphamide, adenovirus, or BK/polyoma virus reactivation) or from fungal infection in the collecting system.

Figure 2: Time course for development of renal failure after HCT[13]



ATN = acute tubular necrosis; HRS = hepato-renal syndrome; VOD = veno-occlusive disease; TMA = thrombotic microangiopathy; CNI = calcineurin inhibitors.

Adapted from Zager RA with permission[13]

Veno-occlusive Disease

Hepatorenal syndrome is among the most common serious renal complications after myeloablative HSCT and the majority are due to veno-occlusive disease (VOD).[3] VOD is a conditioning-related toxicity usually associated with regimens including cyclophosphamide, busulfan, and/or total body irradiation (TBI).[16] The pathophysiology of VOD involves hepatic endothelial and sinusoidal damage causing non-thrombotic sinusoidal obstruction, portal hypertension, and microvascular intrahepatic porto-systemic shunting. The incidence of VOD varies according to the diagnostic criteria used and ranges between 5% and 70%, although severe cases are uncommon.[17,18]

Clinical features of VOD include weight gain, painful hepatomegaly, and jaundice. Conditions that mimic VOD include acute hepatic GVHD, sepsis, or drug-induced cholestasis, CNI toxicity, gall bladder disease, and use of total parenteral nutrition.[18] Timing of symptom onset aids in diagnosis: VOD generally appears during the first 30 days post-HSCT. In the early stages of the syndrome, sodium retention predominates with consequent weight gain, edema, and ascites. Jaundice and right upper quadrant pain follow. Abdominal ultrasound with Doppler may show reversal of flow in the portal vein. ARF often arises, precipitated by renal insults such as sepsis or nephrotoxins. Roughly 50% of those with VOD develop ARF, but some degree of renal insufficiency exists in every patient.[6,19] Severity of disease varies. In mild to moderate cases, hepatic injury is self-limited and symptoms may be treated with analgesia and diuresis and the syndrome eventually resolves completely. Severe VOD consists of progressive hepatic failure accompanied by renal failure and carries a mortality approaching 100% by day 100 post-HSCT.[20]

VOD-associated renal failure is clinically indistinguishable from hepatorenal syndrome. Patients are oliguric with very low fractional excretion of sodium. Total body sodium and water overload are common. Patients generally have low blood pressures, may have hyponatremia, and usually have a bland sediment, although later in the course of the disease, high bilirubin concentrations may cause tubular damage with granular casts. Biopsy and

autopsy studies have confirmed that kidneys do not have structural lesions in VOD, consistent with the notion that the renal injury in hepatorenal syndrome is hemodynamic.[21]

Treatment of severe VOD and ARF is primarily supportive. Maintenance of intravascular volume is of paramount importance. The hematocrit should be maintained above 35% and intravenous albumin should be avoided as it accumulates in extravascular space. Sodium restriction and diuretics are necessary, the latter often as a continuous infusion. Paracentesis for ascites and lactulose for encephalopathy may be required. When renal replacement is indicated, continuous therapies are advantageous due to the very high daily obligate fluid intake in HSCT patients. Defibrotide, a single stranded polydeoxyribonucleotide[22,23] that has fibrinolytic, antithrombotic and anti-ischemic properties is being evaluated for the treatment of established VOD. Initial results are promising and prospective trials are underway to evaluate its efficacy in the prophylaxis and treatment of VOD.

Glomerular disease after HSCT

Nephrotic syndrome is a well-described, but unusual complication of HSCT. It is often associated with chronic GVHD and generally presents at least 6 months post-transplant. The most common etiology is membranous nephropathy, comprising about 75% of cases of nephrotic syndrome.[24,25] This association suggests that post-HSCT nephrotic syndrome may represent a form of renal GVHD. In support of this hypothesis, there is often a temporal correlation between tapering of immune suppression and the development of both GVHD and nephrotic syndrome. In a recent study, Srinivasan et al reported an unexpectedly high incidence of nephrotic syndrome in a series of non-myeloablative HSCT recipients. Among 163 consecutive transplants, they found 7 cases of nephrotic syndrome for a cumulative incidence of 6.1%.[26] Four of these patients underwent renal biopsy that showed membranous nephropathy. Most cases did not respond to increased immunosuppression and 3 went on to end-stage renal disease (ESRD).

Whether non-myeloablative protocols confer a higher risk of nephrotic syndrome than myeloablative protocols has not been studied. The earlier withdrawal of immunosuppression in non-myeloablative HSCT could heighten susceptibility to immune-mediated glomerular disease. Because non-myeloablative transplants result in host/donor marrow chimerism, the persistence of host lymphocytes surviving conditioning is another factor that could increase susceptibility to nephrotic syndrome. These questions certainly deserve further study. Minimal change nephrotic syndrome is also reported after HSCT. This has also been linked to GVHD, but there are fewer cases so no firm conclusions may be drawn.[25,26]

Chronic kidney disease after HSCT

CKD is a recognized and important long-term complication of HSCT, developing in 15%-20% of allogeneic HSCT recipients.[13] With 100,000 survivors of HSCT who received their graft at least 5 years ago alive today the overall burden of CKD in survivors of allogeneic HSCT represents a significant future public health problem.[28] The recent growth of non-myeloablative protocols may actually increase the incidence of CKD in HSCT survivors despite its milder conditioning regimen. Weiss and colleagues recently performed a retrospective cohort study in 122 patients who underwent non-myeloablative HSCT. They determined that 66% had CKD within 1 year of transplant, defined as a ≥25% reduction in baseline GFR (calculated by the abbreviated modified diet in renal disease equation). Twenty-two per cent had a ≥50% reduction in GFR at 6 months. New or worse hypertension was found in 72% of survivors, but anemia was not associated with CKD in this population. Independent risk factors for development of CKD included ARF in the first 100 days, previous autologous HSCT, CNI use, and chronic GVHD.[29] The high rate of CKD in this population, despite the milder conditioning regimen, likely reflects the older age of this patient population and increased baseline comorbidities such as hypertension, cardiovascular disease, diabetes, and baseline renal insufficiency.

In contrast with non-myeloablative HSCT, the majority of cases of CKD after myeloablative allogeneic HSCT are caused by a low-grade renal TMA. This syndrome has also been called bone marrow transplant nephropathy or radiation nephropathy and it resembles hemolytic-uremic syndrome.[28] Characteristic clinical features include slowly rising plasma creatinine, hypertension, and disproportionate anemia. However, some cases have a more fulminant presentation. Urine dipstick shows variable proteinuria and hematuria. This chronic TMA may manifest on prior laboratory tests as low-grade microangiopathic hemolysis with elevated plasma lactate dehydrogenase, low serum haptoglobin, thrombocytopenia, anemia, and sometimes schistocytosis. Renal imaging is usually unremarkable. Kidney biopsy is rarely required – unless the presentation is very atypical – as the lab features are often suggestive. Biopsy carries increased risk in this patient population and biopsy findings are unlikely to significantly alter management. Typical histology includes mesangiolysis, basement membrane duplication, glomerular endothelial cell swelling, and tubular injury with interstitial fibrosis.[30]

The pathogenesis of TMA after HSCT is poorly understood, but renal endothelial damage plays a central role. The conditioning regimen – particularly the irradiation – is a primary cause of renal endothelial damage with post-HSCT factors such as GVHD, infections, and medications (eg, CNIs) playing a later modulatory role.[31] Risk factors for development of TMA syndromes post-HSCT include dose of radiotherapy and use of concurrent cytotoxic chemotherapy.[32] Sirolimus, when added to CNI therapy for GVHD prophylaxis, is associated with a higher incidence of TMA but, fortunately, this is often reversible.[33] Renal shielding during TBI is somewhat protective.[34] Because evidence indicates that ACE inhibition is useful in the treatment of HSCT-related TMA,[35] Cohen and colleagues are prospectively evaluating whether captopril treatment after HSCT may also afford protection against development of this complication.[36]

Chronic CNI toxicity

Moderate-to-severe GVHD carries a mortality rate of 10%-50%,[37] but methotrexate, cyclosporine, and tacrolimus reduce the incidence of both acute and chronic GVHD after allogeneic HSCT. In patients that do not develop GVHD, the CNIs are discontinued 6 months after HSCT and are, therefore, unlikely to play any role in promoting CKD. Fifty percent of transplant recipients do develop chronic GVHD, however, and require long-term immunosuppression (average of 23 months).[2] Long-term use of CNIs after HSCT in this setting certainly contributes to CKD; this has been well-described in non-renal solid organ transplantation and autoimmune disease.[38] It is likely that, in some cases, CNIs also exacerbate the TMA that can arise after HSCT (CNI-induced TMA has been well described after kidney transplantation, for example) or perhaps contribute to development of focal and segmental glomerulosclerosis, but this has not been systematically examined.[39,40]

Management of HSCT-related CKD

Important aspects of the patient's history include the type of HSCT, the conditioning regimen (in particular, was total body irradiation used and at what dose), and the degree of exposure to nephrotoxins (for example, prolonged treatment with amphotericin). Physical examination frequently shows hypertension, hypervolemia, and skin GVHD. Blood tests should be carefully reviewed and repeated to assess for TMA – it should be noted that laboratory features are often intermittent and not florid. Renal ultrasound is often used to exclude post-renal causes, but other imaging studies are rarely required.

General treatment should be as recommended for any CKD patient.[41] Control of hypertension is especially important in patients with a TMA syndrome to reduce endothelial damage. ACE or angiotensin receptor blockade retards progression in animal models of radiation nephropathy and should be used if possible.[35] Hyperkalemia may be more common in this setting than in patients with other forms of CKD and require treatment with a low potassium diet, diuretics, and low-dose sodium polystyrene, if tolerated.[42] Diuretics are frequently required. Anemia may be more severe than expected for the degree of renal insufficiency and should be treated with erythropoietin. It is worthwhile minimizing CNI dosage – if possible - as is sometimes done in solid organ transplantation.[38] There is no evidence that plasma-exchange is beneficial, although it is occasionally used in very severe cases of TMA after HSCT.[43]

End-stage renal disease after HSCT

A subset of patients progress to ESRD and, overall, these patients have worse survival on hemodialysis than patients with ESRD from other causes. In one case-control series, patients starting dialysis after HSCT had a higher mortality than patients with diabetes after matching for age and start-date of dialysis.[44] Renal transplantation is a good option for eligible patients, and those who receive a renal allograft from the same donor as their original HSCT will need minimal or no immunosuppression due to immunologic tolerance of the allograft.[45]

Conclusion

Advances in transplant protocols and supportive care over the last 2 decades have driven impressive growth in HSCT. The rising number of transplants, coupled with an increasing fraction of older and sicker patients being transplanted, mean that HSCT-related renal toxicity will remain an important complication of this life-saving procedure.

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Upcoming Scientific Meetings

15-19 September 2006
28th Annual Meeting of the American Society for Bone and Mineral Research
Philadelphia, PA
CONTACT: www.asbmr.org

14-19 November 2006
ASN Renal Week 2006
San Diego, California
CONTACT: www.asn-online.org

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