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Chronic Kidney Disease after Pediatric Hematopoietic Cell Transplant

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EPIDEMIOLOGY

The cumulative incidence of chronic kidney disease (CKD) varies from 13%-60% in adult studies [1-3] to as high as 62% in children [4]. CKD usually becomes apparent 6-12 months after hematopoietic cell transplant (HCT), although it has been described as early as 2 months and as late as 10 years posttransplant. There are 3 distinct clinical manifestations of renal disease that can occur in the HCT patient: thrombotic microangiopathy (TMA), typically hemolytic uremic syndrome (HUS), and idiopathic CKD and nephrotic syndrome.

RISK FACTORS FOR TMA AND HUS AFTER HCT

Although no clear relationships have been found to date for the development of TMA after HCT, a number of risk factors have been examined. In earlier studies, where HUS was the primary diagnosis, risk factors identified were total-body irradiation (TBI) [1,4-6] and calcinuerin inhibitor use [1,7-12]. However, in more recent studies of TMA, acute GVHD (aGVHD) grades II-IV, older age, and transplant from an unrelated donor are the primary risk factors identified [13,14]. Other investigators have identified sinusoidal obstruction syndrome, matched unrelated donors or haploidentical donors, and lymphoid malignancy as significant predictors of TMA after HCT in addition to the above risk factors [2,15-17]. However, in children who develop HUS after HCT, the presumptive risk factor in these studies has been TBI used as part of the conditioning regimen. For example, Tarbell et al [4] studied 44 children (aged 3-15 years) with ALL or neuroblastoma (NB) who underwent HCT. Twenty-nine of these patients were alive and in remission 3 months after HCT and were evaluated in the study. Eleven patients developed increases in BUN and creatinine, and 10 were anemic and thrombocytopenic with evidence of hemolysis on peripheral blood smear; they also had elevated LDH levels. In every patient except one, the hemolytic process resolved, yet the renal insufficiency persisted. The pathologic findings of mesangiolysis with intraglomerular capillary aneurysm formation in conjunction with the laboratory abnormalities support the diagnosis of HUS in these children. In another small study, Antignac et al [5] described 7 children referred to their nephrology clinic with renal insufficiency approximately 5-10 months after TBI followed by HCT. All 7 children had leukemia and all received cyclophosphamide alone, or with cytosine arabinoside and vepeside, in addition to single-dose TBI as part of their conditioning regimen. Three patients developed chronic renal insufficiency without hypertension. Four of the 7 developed HUS with severe hypertension and microangiopathic hemolytic anemia. Of these, 2 had normalization of their renal function. Follow-up biopsies, however, showed extensive scarring of the renal parenchyma but almost complete resolution of the mesangiolysis. The glomeruli were globally sclerotic, ischemic, or demonstrated mesangial hypercellularity. Thus, there was evidence of persistent and progressive renal damage in these patients despite normalization of serum creatinine and urinalysis. The occurrence of two different clinical presentations but similar pathology in these children further supports the notion that this is a spectrum of disease rather than distinct pathophysiologic processes.

IDIOPATHIC CKD

Idiopathic CKD in this patient population is usually defined as an elevated serum creatinine or an abnormal glomerular filtration rate (GFR) 6-12 months after transplant. The incidence of idiopathic CKD in children after HCT varies from 11%-41% [18-21]. In one recent study, the incidence of CKD (GFR <70 mL/min/1.73 m^2) changed over time, with 41% of children having CKD at 1 year, 31% at 3 years, and only 11% of patients had CKD 7 years after transplant [21]. In approximately 19% of patients,

hematuria and proteinuria persisted out to 10 years after HCT. Berg and Bolme [22] followed 44 children with ALL, AML, and severe aplastic anemia (SAA) and found a significant decrease in GFR 1-2 years after HCT when compared to their baseline GFR (ALL and AML groups) or to a healthy control group, despite serum creatinines that remained within normal limits. An initial decrease in GFR was followed by stabilization up to 5 years posttransplant. Proximal tubular dysfunction has also been described in 14%-45% of pediatric patients 1-2 years after HCT [23]. In this same study, GFR measured by inulin clearance, was significantly lower than prior to transplant, but remained within the normal range 2 years later.

RISK FACTORS FOR IDIOPATHIC CKD

The risk factors for idiopathic CKD in children are similar to those identified in adult studies. Kist-van Holthe et al [24] also retrospectively identified risk factors for the development of both acute and chronic renal insufficiency in a cohort of 142 children undergoing transplant over a period of 5 years in The Netherlands [24]. All children received allogeneic transplants. Ninety-one children received radiation, and 82 of these 91 received TBI. Twenty-five children (18%) had CKD (defined as a GFR <85 mL/min/1.73 m^2). These authors found no correlation between radiation dose used and renal insufficiency at 1 year. In a later study from the same group, only acute renal insufficiency predicted the later development of CKD in patients after HCT [20]. These studies contradict others in the literature that found TBI to be associated with renal injury [18,19,25]. However, the doses used here (5-8 Gy in a single fraction) were much lower than described elsewhere.

In a study of 92 pediatric HCT patients by van Why et al [18], late renal insufficiency developed in 18 of 64 (28%) patients; in half of these patients, the renal disease persisted for 3 months to 3 years [18]. Amphotericin B use, cyclosporine, and TBI were associated with the later development of CKD.

In a large retrospective review of 1635 children and adults, risk factors for the development of CKD after HCT included acute renal failure, aGVHD, and chronic graft-versus-host disease (cGVHD) [2]. In this study, TBI was not associated with development of CKD.

NEPHROTIC SYNDROME AFTER HCT

Chronic GVHD may manifest itself in the kidney as nephrotic syndrome with or without renal insufficiency (reviewed in [26]). Patients usually present with proteinuria, edema, and hypoalbuminemia. The majority of these case reports demonstrated membranous nephropathy (MN) with subepithelial deposits on biopsy; it is postulated that these deposits are antigen/antibodies complexes representing GVHD in the kidney. However, cases of minimal change disease (MCD), which is thought to be a T cell-mediated process, have been described [26]. Comparisons between case reports of membranous nephropathy and minimal change disease after HCT found that membranous nephropathy occurs in 61% of cases compared to 22% of cases having MCD [27]. The majority of reported patients with membranous nephropathy were slightly older males, and had a history of aGVHD and cGVHD. Both MCD and MN occur later after transplant at 8 and 14 months, respectively, and tend to occur within 1-5 months of the development of GVHD and/or the tapering of immunosuppression for their cGVHD. Membranous nephropathy is more difficult to treat with only 27% of patients reported achieving remission compared to 90% of patients with MCD [27]. Others have reported cases of diffuse proliferative glomerulonephritis, ANCA-related glomerulonephritis, focal segmental glomerulosclerosis, and IgA nephropathy [28-32] occurring after HCT. The development of each of these diseases seems to be associated with cGVHD and/or the tapering of immunosuppression. Treatment with high-dose prednisone and/or reinstitution of calcinuerin inhibitors usually results in resolution of nephrotic syndrome. Some physicians have used rituximab successfully in patients with nephrotic syndrome after HCT, typically in cases of membranous nephropathy [33].

MANAGEMENT OF CKD AFTER HCT

Patients who develop CKD after hematopoietic stem cell transplants are at increased risk of mortality [34]. Based on animal models of HCT and specifically of radiation-induced HUS, there are potential interventions for patients with HUS after HCT. Angiotensin-converting enzyme inhibitors (ACEI) have been used in rodent models of HCT-related renal injury. The use of captopril or enalapril at the time of TBI in these animals resulted in less azotemia, lower blood pressures, and long-term preservation of renal function [35]. ACEI and antiotensin receptor blockers (ARBs) also help to reduce inflammation and inflammatory markers in patients after transplant [36,37]. These agents have also been shown to slow progression of CKD in patients with renal disease from various causes [38,39]. However, these mouse models were of radiation induced injury and because it is likely that TBI is not playing a role in idiopathic CKD, it may be that the potential beneficial effects of ACEI and ARBs in these patients are their potential to reduce blood pressure as well as inflammation and inflammatory markers in patients. Randomized controlled trials using ACEI or ARB have not yet been published in people undergoing HCT, although a trial is currently underway.

Management of patients with ESRD after transplant may include the use of peritoneal and/or hemodialysis. Caring for these patients also involves management of the complications associated with ESRD which include anemia, bone disease, hypertension, and metabolic abnormalities. There have been case series of patients undergoing renal transplantation successfully after HCT, and it is a viable option for patients with end-stage renal disease after HCT [40-42]. In patients who received their kidney from the same donor as their stem cells, little or no immunosuppression is required.

SUMMARY

There are 3 clearly distinct clinical entities that occur after HCT: TMA, idiopathic CKD, and nephrotic syndrome. The potentially independent role of GVHD and chronic inflammation in the development and progression of idiopathic CKD warrants further investigation. CKD after HCT is a relatively common occurrence. As the indications for and number of transplants performed world wide increases, so will the burden of kidney disease. Identifying those patients at risk for the development of CKD will be important for potential intervention and prevention of CKD and progression to end-stage renal disease in this patient population. There are those patients who will develop CKD that is not related to TBI or the conditioning regimen but rather to complications and/or therapy that occur after HCT, specifically aGVHD and cGVHD and prolonged calcinuerin inhibitor use. The burden of management will fall not only to the nephrologists but the oncologist as well to ensure close monitoring of renal function, blood pressure, and urinalyses posttransplant. It may be that our energies have been misdirected in trying to reduce exposure to TBI, and rather we should try to decrease the inflammatory and cytokine effects of GVHD and reduce exposure to calcineurin inhibitors to prevent CKD in this population of patients.

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