REVIEW ARTICLE

Perspectives, therapy, and etiology of kidney impairment following hematopoietic cell transplantation

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Wright S, Pasco J, Williams L et al. Perspectives, therapy, and etiology of kidney impairment following hematopoietic cell transplantation. J Kidney Treat Diagn 2023;6(1):1-3.

ABSTRACT

Hematopoietic Cell Transplantation (HCT) frequently results in kidney dysfunction, which has been shown to have a detrimental effect on both short and long term mortality. This complication has numerous, frequently overlapping, and poorly understood causes. Management therefore calls for multifaceted research and concurrent treatment of potential causes. Due to a lack of precise markers and the high prevalence of renal biopsy contraindications among HCT recipients, the etiology is typically left unexplained. Here, we offer a synopsis of the pathogenesis and suggest an approach for assessing kidney damage following HCT. We also identify the most critical research directions that should be pursued in order to identify people at risk for severe renal injury and create nephroprotective measures.

Keywords: Acute kidney injury; Chronic kidney disease; Hematopoietic cell transplantation; Kidney dysfunction; Renal biopsy

INTRODUCTION

Over 50,000 Hematopoietic Cell Transplants (HCTs) are carried out worldwide each year. Statistics from the European society for Blood and Marrow Transplantation (EBMT) show that transplant recipients are becoming more common and that their survival rates are improving. Although Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD) following HCT are less common now than they were in the past, these complications nevertheless have a substantial impact on the survival and quality of life of transplant recipients. To create safer transplantation processes, it's crucial to identify risk factors, analyze causes, and treat kidney injury as soon as possible [1].

AKI after HCT is often characterized as a rise in serum creatinine levels from the baseline level and/or a 50% decrease in Glomerular Filtration Rate (GFR) within the first 100 days following HCT. According to the criteria of the Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO) or the stadium of injury in Risk, Injury, Failure, Loss, End stage (RIFLE), AKI of at least this stage has been shown to be a poor predictor of long term mortality. Depending on the type of conditioning used after allogeneic HCT (alloHCT), such defined AKI occurs in 12%–21% of patients receiving autologous HCT (autoHCT) and varies from 36%–56% after myeloablative conditioning to 7%–46% after Reduced Intensity Conditioning (RIC). According to reports, 7%, 20%-33%, and 4% of individuals with AKI need Renal Replacement Therapy (RRT), accordingly. Comparisons between studies are difficult because to the heterogenicity of the examined groups and the variable definition of AKI in the HCT literature. AKI is associated with increased All Cause Mortality (ACM) and nonrelapse mortality, independent of criteria and laboratory techniques used to assess kidney function [2].

While the median period for the incidence of AKI ranges from 20 to 40 days, a study conducted by researchers revealed that the formation of AKI prior to engraftment is associated with significantly shorter overall survival within 100 days following HCT, at 56% versus 90%, respectively. AKI after HCT may be difficult to diagnose. In relation to muscle mass, hydration, and latency (between one and three days following nephron injury), serum creatinine concentration rises. Similar flaws exist in the estimate of GFR based on creatinine levels. Patients who were eligible for HCT had significantly different estimated and radioisotopic GFR measurements (using iohexol and Tc-99m-diethylenetriaminepentaacetic acid). As a result, both under and overestimations of GFR increase the possibility of toxic or insufficient chemotherapy dosages as well as delayed AKI diagnosis. There is an urgent need for novel kidney function markers that are more sensitive and precise because radioisotopic approaches are costly and time consuming [3].

HCT comorbidity index is a helpful measure for AKI prognosis (HCT-CI). It has been demonstrated that HCT-CI 1-2 is linked to a 2.4 fold greater risk of severe AKI while HCT-CI 3 nearly doubles the risk [4].

A GFR decline that lasts for at least three months and drops below 60 mL/min/m^2 is referred to be CKD. Up to 4.5% of patients were found to develop CKD within five years of receiving an HCT, and 7% of these patients went on to develop end stage renal failure and require RRT. After HCT, the prevalence of CKD rises over time and varies significantly between allogeneic (14%) and autologous (4%) transplant recipients. AKI in the early post transplantation period, Total Body Irradiation (TBI) as a conditioning treatment, and the presence of graft versus host disease have all been identified as risk factors (GvHD), Urinary albumin to creatinine ratio, or ACR (30 mg/g–300 mg/g), is a poor predictive indicator for survival, CKD progression, the development of GvHD, and bacteremia. During the first 100 days following HCT, there is a linear relationship between the level of ACR and NRM: Mortality increases by around 10% for every 100 mg/g ACR increase [5].

Prior to transplantation, many HCT candidates had compromised kidney function. Comorbid conditions, underlying disorders, or both may be to blame for this. Glomerulonephritis is a paraneoplastic syndrome that arises in many hematological malignancies and goes away when the underlying illness goes into remission. Monoclonal protein buildup in nephrons causes cast nephropathy, glomerulonephritis, or, less frequently, amyloidosis in multiple myeloma and other plasma cell dyscrasias. Additionally, renal interstitial tissue is directly harmed by hypercalcemia [6].

Other malignancy related mechanisms of kidney damage include tumor lysis syndrome, Cytokine Release Syndrome (CRS), cancer cell infiltration, and obstructive uropathy brought on by lymphadenopathy. It's important to consider iatrogenic harm caused by radiation and chemotherapy as well. Pretransplant renal insufficiency is also a result of comorbid conditions such diabetes mellitus, hypertension, and arteriosclerosis. In contrast to patients without any of the aforementioned disorders, patients with moderate CKD and cardiovascular disease (including coronary disease, cerebral

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Received: *01-Nov-2022, Manuscript No. PULJKTD-22-5530*; **Editor assigned**: *03-Nov-2022, PreQC No. PULJKTD-22-5530 (PQ)*; ***Reviewed:*** *17-Nov-2022, QC No. PULJKTD-22-5530*; ***Revised:*** *02-Jan-2023, Manuscript No. PULJKTD-22-5530(R)*; ***Published:*** *10-Jan-2023, DOI: 10.37532/PULJKTD.23.6(1).1-3*

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atherosclerosis, and diabetes) have a decreased risk of developing AKI after alloHCT. The cause of this is unclear, however it may be related to cholesterol's cytoprotective actions and statins' and antihypertensive drugs nephroprotective qualities [7].

Although CKD is not a clear contraindication for alloHCT, RIC is preferable in this patient population. Studies on individuals who underwent transplantation after RIC and had mild to moderate CKD did not reveal an increase in mortality. Myeloma patients with end stage renal failure who are receiving RRT undergo auto HCT with manageable transplant related mortality, but a dose decrease of melphalan is necessary. Patients without renal insufficiency have a transplant related death rate of around 1%, whereas those with renal impairment had a rate of up to 4%.

LITERATURE REVIEW

Prerenal AKI

Prerenal AKI can happen before, during, or after HCT. If remission was not obtained prior to conditioning, this may be the result of fluid loss brought on by chemotherapy induced vomiting or diarrhea, iatrogenic fluid overload, and tumor lysis syndrome. Capillary Leak Syndrome (CLS) and engraftment syndrome are two additional issues that result in AKI in the early post transplant period. Both fluid retention and non-infectious fever are produced by the release of proinflammatory cytokines and may appear after autoHCT and alloHCT. Prerenal secondary to intravascular volume depletion and maybe also having a direct impact on kidney tissue is the mechanism of kidney injury [8].

Within two weeks of HCT, CLS frequently manifests as diuretic resistant peripheral edema and serosal effusion. In the area of haploidentical HCT, CLS as a part of CRS merits special consideration. In this situation, 87% of patients are complicated by CRS, and 12% of those instances have severe CRS, which is associated with much increased mortality. In 14% of cases with severe CRS, clinically significant renal failure was discovered. Steroids and currently being researched anti-interleukin-6 medications are available as treatments. The symptoms of engraftment syndrome resemble those of CLS, however they typically occur during neutrophil regeneration and are frequently accompanied by fever, rash, and multiorgan failure.

8% of alloHCT recipients and 27% of autoHCT recipients had kidney impairment in engraftment syndrome. Treatment with glucocorticoids for engraftment syndrome works effectively when started promptly [9].

Conditioning

It is challenging to determine how a certain medication or conditioning regimen would affect renal damage given the diversity and complexity of conditioning regimens. Additionally, kidney damage may take time to emerge, which is especially important when TBI use is involved.

TBI

Kidney damage brought on by TBI is particularly prone to manifest years after exposure. Glomerulosclerosis symptoms, blockages in the glomerulus arteries, and scarring of the renal parenchyma are visible in animal models and autopsy investigations. Asymptomatic course, proteinuria, thrombotic microangiopathy, and end stage renal disease are some examples of the clinical presentation. Radiation dosage fractionation into five to twelve sessions and partial kidney shielding may reduce renal toxicity, albeit at the cost of greater recurrence rates. Angiotensin convertase inhibitors may protect kidney function during TBI, according to animal studies and limited cohort data, but further research is required to reach definitive results.

DISCUSSION

Chemotherapy

Chemotherapeutics that are either nephrotoxic or removed by the kidneys and employed in conditioning regimens. The American society for blood and marrow transplantation's document and recommendations for the general public both contain suggestions for dose changes. The majority of the information in the second study, which is just for HCT recipients, comes from short studies and case reports.

Fludarabine, which is frequently used in RIC regimens for individuals with comorbidities such renal insufficiency, is the focus of a study. Fludarabine is not nephrotoxic, but because it is removed by the kidneys, those with renal impairment are more likely to experience neurotoxic side effects. It has been established that the concentration and clearance of F-Ara-A, the active metabolite of fludarabine, correlate with creatinine clearance and that a high plasma concentration of F-Ara-A (in parallel with a low clearance) correlates with a higher NRM in HCT recipients, whereas a high clearance entails a higher risk of GvHD. As a result, accurate dosage is essential for the effectiveness and safety of treatment, although current recommendations call for the same dose reduction across a wide range of GFR. As a result, current research focuses on developing tailored dose calculations based on measurements of body size and renal function.

GvHD prevention

It has been established that some medications used to treat and prevent GvHD raise the danger of renal damage. CNIs require special consideration due to their multiple nephrotoxic effects. This could lead to both irreversible renal failure and a drop in GFR due to secondary vasoconstriction, which is reversible after CNI dose reduction or withdrawal. A link between Cyclosporine (CSA) medication and AKI was found in one third of the 19 investigations of alloHCT, with only a few researches demonstrating a concentration dependent effect.

However, prolonged CSA therapy poses a considerable risk for developing CKD. Tacrolimus serum levels and the onset of AKI are correlated, according to a recent study in RIC HCT. Studies comparing procedures with tacrolimus or CSA did not find any differences in nephrotoxicity or efficacy in GvHD prevention. A study comparing post transplant cyclophosphamide with CNI based regimens demonstrated that new CNI-free regimens for the prophylaxis of GvHD might also be a milestone in reducing post HCT kidney injury: Creatinine concentration was similar to the baseline level 1 year after HCT in the post transplant cyclophosphamide group, whereas the median fold change in the CNI based group was 1.4.

Transplant associated microangiopathy

Atypical hemolytic uremic syndrome is similar to the complex and poorly understood condition known as Transplant Associated Microangiopathy (TAM). It is believed that vascular endothelial injury causes platelet aggregation in the microvasculature and over activation of the complement, which results in thrombosis and the deposition of fibrin. High dose radiation exposure, viral infections (cytomegalovirus, adenovirus), GvHD, VOD/SOS, and CNI therapy are risk factors. TAM typically manifests as thrombocytopenia, neurological symptoms, organ failure, and hemolytic anemia (with schistocytes in the blood smear, elevated lactate dehydrogenase, and decreased amount of haptoglobin). The most common organ affected is the kidney, and autopsy investigations support TAM characteristics in patients with normal creatinine levels as well. There is no standard set of TAM diagnostic criteria.

The blood and marrow transplant clinical trials network's consensus on renal function testing includes a twofold increase in creatinine or at least a 50% decrease in GFR.

CONCLUSION

Renal function testing is not one of the criteria specified by the EBMT international working group. It is advised to confirm the diagnosis of TAM

with a kidney biopsy whenever practical because all of the criteria listed in the guidelines are ambiguous and frequently satisfied because of an underlying ailment, the toxicity of treatment, an infection, or drugs. Complement component evaluation, antibodies against complement factor H, and results specific to the damaged organs, like pulmonary hypertension or anomalies in the central nervous system, are examples of noninvasive diagnostics. Intestinal biopsy is a possibility in cases of gut dysfunction.

Additionally, it is advised to take TAM into account when microalbuminuria and hypertension are initially detected. AKI, proteinuria >30 mg/dL, and elevated C5b-9 complement complex concentration are all poor prognostic indicators.

A kidney damage prevention strategy

Simple steps, such as tight fluid electrolyte control, appear to be the key to preventing kidney damage. Therefore, it should be routine procedure in transplantation centers to regularly monitor weight, fluid balance, blood pressure, electrolytes, and creatinine. Drugs that are nephrotoxic should only be taken very sparingly. High hopes are attached to research on novel markers of kidney injury because they are essential for early diagnosis, treatment, and prevention of AKI. They ought to make kidney damage easier to identify and accurately quantify. Additionally, finding subclinical kidney disease before HCT may help doctors select less nephrotoxic conditioning and GvHD prevention regimens.

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