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CHOROBY NEREK U PACJENTÓW PO PRZESZCZEPIENIU SZPIKU

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure used in the treatment of hematological diseases. Approximately 60,000 procedures are performed annually around the world. Thanks to modern treatment, the survival rate of patients after HSCT has significantly increased, but they are exposed to numerous complications. One of these complications is chronic kidney disease and acute kidney injury, which can lead to end-stage kidney failure. Chronic kidney disease may be secondary to chemotherapy and radiotherapy after transplant, including toxic conditioning and complications.

The aim of this study is to present and better understand the of renal complications after bone marrow transplantation. Also methods of preventing and limiting the severity of these complications will be presented.

Acute kidney failure (AKI) is a common complication of bone marrow transplantation. It is estimated to occur in 20% to 75% of HSCT patients. The risk of AKI depends on the type of transplantation and conditioning regimen. It should be noted that the epidemiology and prognosis of renal failure vary depending on transplantation procedures.

Patients who required high-dose chemotherapy and total body irradiation are more likely to suffer from nausea, vomiting, and diarrhea, which may contribute to the development of prerenal AKI. Renal AKI may be caused by sepsis, a drug toxicity that causes interstitial nephritis. Infections of viral etiology, including adeno-polyomaviruses causing hemorrhagic cystitis, may be the cause of extrarenal AKI. The incidence of AKI in autologous HSCT is much lower than after allogeneic stem cell transplantationwhich may be related no occurrence of GVHD.

Chronic kidney disease (CKD) is also often diagnosed and treated as a complication after bone marrow transplantation. According to data from the literature 6-12 months after allogeneic HSCTapproximately 20% of patients develop CKD. This is caused by many factors. The risk factors for the development CKD include older age, female sex, and use of nephrotoxic drugs (including cytostatics, e.g. fludarabine, etoposide, anti-infective drugs; amphotericin B, and calcineurin inhibitors). Radiation nephropathy is the cause of late renal dysfunction, confirmed in approximately 20 % of patients. Radiation damages the vascular endothelium and causes hemolysis. It should be emphasized that chronic graft versus host disease (cGVHD, chronic graft versus host disease), which directly affects the development and advancement of CKD, is the most common late complication of allogeneic hematopoietic cell transplantation.

In patients after HSCT should be emphasized that the development of glomerulopathy and nephrotic syndrome, which are rare symptoms of non-classic chronic graft-versus-host disease. There are few reports in the available literature about cases of glomerulonephritis and nephrotic syndrome. The etiology and pathogenesis of nephrotic syndrome after HSCT in patients with GVHD remains unclear. The most common histological diagnoses are membranous nephropathy and minimal change disease. On average, nephrotic syndrome develops approximately 24 months after HSCT.

In our work, we conducted a study aimed to identify early markers of acute kidney injury in patients after allogeneic bone marrow transplantation.Initially, we studied 80 patients after allogeneic HSCT and 32 healthy volunteers, in whom we assessed the concentration and mutual ratio of kidney damage biomarkers in urine: IGFBP7 and TIMP2, netrin-1 and semaphorin A2. We assessed the concentration of the above-mentioned markers in subgroups of patients with eGFR below and above 60 ml/min/1.73m^2. Studies have shown that the concentration of the IGFBP7 biomarker was significantly higher in patients with eGFR below 60 ml/min/1.73m^2. The results obtained may contribute to a deeper understanding of the development of kidney damage and emphasize the importance of early diagnosis of kidney failure to prevent later complications. To our knowledge, this study is the first to evaluate the importance of urinary biomarkers in renal injury after HSCT.

In the next study, we expanded the group of patients to 150 people after alloHSCT between 1998 and 2020 due to hematological diseases. Then we divided the above-mentioned patients depending on the underlying disease (acute myeloid leukemia in 45% of patients, acute lymphoblastic leukemia in 19%, mature cell lymphomas in 7%, and others, i.e. myelodysplastic syndrome, chronic myelomonocytic leukemia, aplastic anemia and chronic lymphocytic leukemia, in a total of 29 %) and depending on age (the average age of patients with acute myeloid leukemia is 52 years and patients with lymphoma - 46 years). Data was analyzed retrospectively. CKD stage 3a was diagnosed in 19%, 3b in 4% of patients transplanted for acute myeloid leukemia. In patients treated for acute lymphoblastic leukemia, CKD stage 3a was diagnosed in 18% and 3b in 14%, and in patients with lymphoma, stage 3a was diagnosed in 18%, while CKD stage 3b was diagnosed in 27% of patients. It is noteworthy that none of the studied patients developed stage 4 or 5 CKD. Urinary sediment was also assessed, with erythrocyturia found in 11% of patients and/or proteinuria in 12% of patients.

In another retrospective study, we assessed the relationship between the severity of renal failure and the occurrence of anemia in patients who underwent alloHSCT at least 3

months before the examination. In this study, we analyzed the data of 156 patients who had undergone alloHSCT for hematological diseases more than 100 days earlier (to avoid abnormalities caused by acute GVHD. Anemia was diagnosed in 13% of women and 35% of men. Anemia most often occurred in patients who were treated due to acute myeloid leukemia (55% of women, 30% of men). An important fact is that 56% of women and 17% of men in this group had anemia related to chronic renal failure where GFR was below 60 ml/min/1.73 m^2.

HSCT is an important therapy for many patients with hematological diseases, but it is a toxic therapy, including nephrotoxic therapy. In the presented studies, we analyzed the incidence of renal complications after HSCT, such as acute kidney injury and chronic kidney disease, we looked for characteristic markers of kidney damage in this population of patients, and we assessed the incidence of secondary anemia.We found intercorrelations between specific biomarkers such as the interconnection of semaphorin A2 with netrin-1, IGFBP7 and TIMP2, IGFBP7 with serum creatinine, which may help in further treatment planning, selection of appropriate chemotherapy, conditioning and immunosuppressive treatment after transplantation.