NJSC "Astana Medical University"

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Abstract
of the dissertation work for the academic degree of Doctor of Philosophy PhD
in the specialty 8D10102 – "MEDICINE"

«Evaluation of Kidneys' Functional State in Acute Leukemia Patients after Hematopoietic Stem Cell Transplantation»

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ANNOTATION

The relevance of research

Over the past decades, significant results have been achieved in the treatment of patients with acute leukemia due to the optimization of chemotherapeutic treatment protocols, accompanying therapy and bone marrow transplantation [Rose-Inman H.,2017].

In many countries of the world, including Kazakhstan, bone marrow transplantation is performed in patients with acute leukemia from a high risk group with a tendency to increase the number of transplants worldwide, as demonstrated by numerous studies [Niederwieser D., 2016].

Bone marrow transplantation (BMT) is the only chance to prolong life and life-saving therapy for patients with acute leukemia, after which, unfortunately, complications may occur due to the transplantation procedure itself [Coppell J.A., 2010; Hingorani S., 2016; Tuzovic M., 2019...].According to world research, in patients who have undergone BMT, kidney damage develops in the early and late posttransplantation periods, clinically manifested by acute renal damage with the possibility of transformation into chronic kidney disease [Wanchoo R., 2019; Jaguar D., 2018; Krishnappa V., 2016...].

In the USA, according to two systematic reviews by S.R. Kanduri and a group of co-authors. It was determined that 58% of patients with hemoblastosis after BMT had renal function restoration after an episode of acute renal injury, and 10% of patients needed renal replacement therapy [Kanduri S.R., 2020]. The authors believe that the incidence of acute kidney injury among patients undergoing BMT remains high and is one of the causes of death in patients [Kanduri S.R., 2021]. The results of the study by Sangeeta R. Hingorani and a group of co-authors. In the USA, with the participation of 1,635 patients with hemoblastosis, it was shown that 23% of patients developed chronic kidney disease after BMT [Hingorani S., 2007; Hingorani S., 2018]. According to a systematic review conducted by M.J. Ellis and a group of co-authors, chronic kidney disease develops in about 16.6% of patients with hemoblastosis who underwent BMT, with a survival rate of 80% of patients 100 days after BMT [Ellis M.J., 2008]. Similar results of the development of chronic kidney disease after BMT in patients with hemoblastosis are described by Shimoi T. [Shimoi T., 2013] and Jo T. [Jo T., 2017] from Japan, Kępska-Dzilińska M. from Poland and Karyne Pelletier from Canada [Pelletier K., 2022]. There are a sufficient number of studies in the world to study the effects of BMT in patients with various types of hemoblastosis, but in Central Asia and the CIS countries there are no studies on renal dysfunction in patients with acute leukemia after BMT.

In this regard, the purpose of this study is to assess the clinical and functional state of the kidneys in patients with acute leukemia after BMT.

The aim of the study was to study the clinical and functional state of the kidneys in patients with acute leukemia before and after BMT with the development of a model for predicting acute renal injury and assessing patient survival.

Research objectives:

1. To analyze clinical and laboratory data before and after BMT in patients with AML and ALL.

2. To investigate the functional state of the kidneys in patients with acute leukemia after BMT.

3. To develop a model for predicting acute renal injury and to analyze the survival rate of patients with acute leukemia who have suffered acute renal injury after BMT.

4. To analyze the survival rate of patients with acute leukemia after BMT.

The object of the study:

The study included 181 patients with ALL and AML after BMT.

Study design: a prospective cohort study.

Research methods:

– clinical methods: collection of complaints, anamnesis of the disease and life, objective examination of organs and systems;

– laboratory research methods;

– general blood test;

– general urine analysis;

– biochemical blood analysis (total protein, albumin, creatinine, urea, potassium, sodium, uric acid, alkaline phosphatase);

– calculation of glomerular filtration rate;

– determination of beta-2 microglobulin in urine;

– determination of the albumin-creatinine ratio;

– ultrasound examination of the kidneys;

– statistical method of processing the received data.

Scientific novelty: For the first time, an assessment of the effect of allogeneic and haploidentical BMT on the clinical course and indicators of protein-electrolyte metabolism in patients with acute leukemia was carried out.

For the first time in patients with acute leukemia, the effect of BMT on kidney function was evaluated in dynamics 30 days, 100 days and 1 year after BMT.

For the first time in the Republic of Kazakhstan, an equation of the prognostic probability of acute kidney injury and an analysis of the survival rate of patients with acute leukemia after BMT has been calculated.

Practical significance:

The results of the study will allow the hematologist and nephrologist to take into account possible periods of deterioration of kidney function after allogeneic and haploidentical BMT in patients with acute leukemia.

The results of this work will allow haploidentical BMT and us to take into account the possibility of the influence of allogeneic on kidney function in patients with acute leukemia. The study of renal markers, such as beta-2-microglobulin, albumin-creatinine ratio, will complement the diagnostic methods of glomerular and tubular renal function in patients with acute leukemia after BMT. Based on the results of the study, the developed prognostic model will allow us to calculate the probability of developing acute renal damage after BMT.

The main provisions submitted for protection:

1. After haploidentical BMT in patients with AML and ALL, 100 days after transplantation, there was a significant decrease in kidney function, total protein and albumin levels.

2. In patients with acute leukemia, the indicators of beta-2 microglobulin and albumin-creatinine ratio after bone marrow transplantation had a significant increase compared with the data before transplantation, while a significant increase in albumin-creatinine ratio in patients with ALL occurred after allogeneic and after haploidentical transplantation, while in patients with AML Leukemia was detected only after haploidentical transplantation.

3. In patients with acute leukemia, acute renal damage after haploidentical bone marrow transplantation developed 3 times more often than in patients with acute leukemia after allogeneic transplantation, and after haploidentical BMT, worse survival of patients was revealed regardless of the type of leukemia.

Conclusions: 1. Patients with ALL (32.1±8.7 years) and AML (33.8±10.6 years) were of young age, almost equivalent in gender ratio (with ALL m-51.6%, w-48.4% and with AML m-52.9%, w-47.1%). In patients with ALL, subtype B2 prevailed (38.71%) with a complication in the form of neuroleukosis ($p=0.02$), in patients with AML - M1-M2 (32.77%), and sepsis ($p=0.013$) and absence of remission ($p=0.002$) were more common.

2. In patients with ALL who underwent BMT, a longer neutrophilic engraftment was revealed after haploidentical BMT ($U=307.5$, $Z=2.437$, $p=0.015$). The analysis of the total protein level was significantly lower after 1 year ($p=0.022$), and the albumin level was significantly lower 100 days after haploidentical transplantation (U 100 days=274, $Z=-1.967$, $p=0.05$) in patients with ALL. In patients with AML, there was a significant decrease in total protein after haploidentical transplantation after 30 days ($p=0.019$) and 100 days ($\chi2=20,802$, $df=3$, $p=0.0001$).

3. In patients with ALL, 30 days, 100 days and 1 year after haploidentical BMT, a significant increase in creatinine levels ($\chi2=10.304$, $df=3$, $p=0.0126$), urea ($\chi2=11.636$, $df=3$, $p=0.009$) and uric acid was detected ($\chi2=11.894$, $df=3$, $p=0.008$) with a decrease in glomerular filtration rate ($\chi2=11.704$, $df=3$, $p=0.008$), while patients with ALL had a significant increase in creatinine levels 100 days after haploidentical transplantation ($U=271.5$, $Z=-1.976$, $p=0.048$).

4. In patients with acute leukemia, the indicators of beta-2 microglobulin (AML $U=113$, $Z=-2.692$, $p=0.007$; ALL $U=99$, $Z=-2.678$, $p=0.007$) and albumin-creatinine ratio (AML $U=104$, $Z=-2$, 984, $p=0.003$; ALL $U=121$, $Z=2,147.$, $p=0.032$) after transplantation had a significant increase compared with the data before BMT.

5. When studying the effect of the type of transplantation, there was a significant increase in the albumin-creatinine ratio in patients with ALL after allogeneic ($Z=-2.032$, $p=0.042$) and after haploidentical transplantation ($Z=-2.810$, $p=0.005$), while in patients with AML, an increase in this indicator was revealed after haploidentical transplantation ($Z=-3.064$, $p=0.002$).

6. In patients with acute leukemia, acute renal damage after haploidentical BMT was detected in 3.8%, while after allogeneic transplantation in 1.1%. The predicted probability of acute renal injury as creatinine variables before transplantation and the type of haploidentical bone marrow transplantation has a statistically significant result ($AUC=0.730$, $p=0.009$).

7. The death rate was 45.2% in patients with ALL and 33.6% in patients with AML. The study of three-year survival of patients showed no significant differences

between the type of acute leukemia ($\chi2=2.048$, df=1, p=0.152) and depending on the type of transplantation ($\chi2=1.689$, df=1, p=0.194), but the worst survival of patients after haploidentical BMT was revealed regardless of the type of leukemia.

Practical recommendations

1. All patients with acute leukemia are recommended to have renal function examined 100 days after BMT, and in patients who have undergone haploidentical transplantation, an additional 30 days later.

2. In patients after haploidentical BMT, renal dysfunction may occur not only after 100 days, but also after 30 days with the possible development of acute renal damage with worse patient survival.

3. An increase in the level of beta-2 microglobulin and albumin-creatinine ratio in the early period after BMT may be predictors of impaired renal function in patients with acute leukemia.

Approbation of the dissertation

The dissertation work was tested at an expanded meeting of the Department of Internal Medicine with courses in gastroenterology, endocrinology and pulmonology (Protocol No. 10A dated July 29, 2023).The main results of the research and the provisions of the dissertation are reported in the speeches:at the XVI Scientific and Practical Conference of Internal Diseases of the Moscow City Scientific Society of Therapists (Moscow, 2022) with the publication of the material in the Russian journal Clinical Gerontology (Moscow, 2022), at the National Nephrological Congress of the Foundation of the Republic of Kazakhstan (Almaty, 2022), at the 10th International Scientific and practical conference "Science and Education in the modern world" (Astana, 2022).

Publications on the topic of dissertation

9 publications have been published on the topic of the dissertation, including 1 article in a publication with the 34th percentile (Q4) on CiteScore in the Scopus database, 4 articles have been published in domestic publications recommended by the KKSON of the Ministry of Education and Science of the Republic of Kazakhstan and 1 article has been published in an international journal. 3 copyright certificates have been received (№23020, №33509, №23185).

Personal contribution of the dissertation

The work was carried out in accordance with the direction of development of science in the field of "Life and Health Sciences" approved by the Higher Scientific and Technical Commission under the Government of the Republic of Kazakhstan. The dissertation independently recruited patients, surveyed study participants, summarized the results of the study, conducted statistical data processing, and wrote articles under the guidance of a supervisor and consultants.

Volume structure and dissertation

The dissertation consists of 116 pages of computer text, which includes an introduction, a literature review, research materials and methods, conclusions and general conclusions. There are 18 tables and 41 figures in the work. The list of references contains 235 sources.