Association of β_2 microglobulin level and glomerular filtration rate in patients with acute leukemia after hematopoietic stem cell transplantation

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ABSTRACT

Hematopoietic stem cell transplantation is a life-saving therapy in patients suffering from acute leukemia. However, kidney complications developed after performing hematopoietic stem cell transplantation can affect the course and prognosis of the disease in patients with acute leukemia. This study is aimed at assessing the functional status of the kidneys in patients with acute leukemia who have undergone hematopoietic stem cell transplantation. The study has observed a group of patients with acute lymphoblastic leukemia and acute myeloid leukemia who have undergone hematopoietic stem cell transplantation. It has been discovered that β_2 microglobulin is a sensitive method of analyzing renal function, with the β_2 microglobulin threshold urine level not exceeding 0.3 mg/L. The complex diagnostics of kidney function in hematopoietic stem cell transplantation recipients has given the opportunity to identify the relationship between increased β_2 microglobulin levels and decreased glomerular filtration rate. It has been determined that β_2 microglobulin is a biomarker of renal disorders. The obtained data have showed that β_2 microglobulin can be used as a diagnostic marker of reduced kidney function.

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Key words: Hematopoietic stem cell transplantation; acute leukemia; β_2 microglobulin; glomerular filtration rate; biomarkers of renal function.

Contributions: AO designed the manuscript structure, organized the literature search, and wrote the first draft. VB, AM, AM, VM contributed to the literature search/revision and to the manuscript writing. VB organized the references editing. BA made the final revision, manuscript editing, and approval. All authors contributed to the article and approved the submitted version.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 17 December 2022.
Revision received: 19 January 2023.
Accepted for publication: 20 January 2023.

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Licensee PAGEPress, Italy
Italian Journal of Medicine 2023; 17:1563
doi:10.4081/itjm.2023.1563

Introduction

Nowadays, hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for treating acute leukemia worldwide.[1,2] The global assessment of hematopoietic stem cell transplantation practices has shown an increase in the number of HSCTs performed over the past 30 years.[3] According to the latest data, more than 1.4 million HSCTs have been performed all around the world, with approximately 70,000 patients with hematological malignancies annually undergoing HSCTs.[4,5] However, HSCT is considered a 'complex' treatment method that causes a number of complications, such as infection,[6] graft *vs* host disease,[7] liver diseases, *etc*.[8] The list of the complications caused by HSCT in patients with acute leukemia includes reduced renal function.[9-12]

It is known that HSCT recipients' renal system is exposed to a number of direct and systemic effects that alter kidney function. Thus, using a high-dose chemotherapy (conditioning regimen) combined with the immunosuppressive preventive treatment of graft *vs* host disease (GvHD), and the frequent administration of antibacterial, antifungal, antiviral agents in agranulocytosis, have nephrotoxic effects on renal tissue.[13] In addition, patients with acute leukemia in-

evitably experience severe complications after HSCT. These complications indirectly affect kidney function.

Studies have shown that reduced kidney function occurs in the early and late periods after HSCT.[14] Due to bone marrow failure occurring prior to the engraftment of transplanted stem cells and patients' high exposure to infections, the early period after HSCT is the most dangerous period for patients with acute leukemia. Early renal dysfunction in patients after undergoing HSCT may be represented by an acute kidney injury caused by a high-dose chemotherapy in the conditioning regimen.[15-18] Kidney dysfunction developed in the late period after HSCT is manifested by a chronic renal disease progressing approximately one year after the performed HSCT.[19]

Diagnosis of the functional status of the kidneys in patients who have undergone HSCT is an important issue for the timely assessment of impaired renal function and the degree of impairment, as well as the assignment of appropriate treatment.[20] The standard determination of glomerular filtration rate based on measuring the level of creatinine serum in patients undergoing HSCT is an accessible and widely used method for studying renal function.[21] When considering other diagnostic methods for examining kidneys, many authors have studied kidney biomarkers, such as β_2 microglobulin, which helps to detect early changes in the kidney tissue. β_2 microglobulin is a component of the major histocompatibility complex I (MHC I) molecule present in all nucleated cells.[22-24] Physiologically, β_2 microglobulin passes through the glomerular membrane. Subsequently, more than 99.9% of the filtered protein is reabsorbed in nephron proximal tubules, with only trace quantities of the substance detected in normal urine.[25] Catabolism of β_2 microglobulin is performed by renal elimination. Therefore, the concentration of this protein in the urine increases when the kidneys are damaged.[26]

Studying renal dysfunction is definitely an important matter in the successful management of HSCT recipients since the severity of complications and the prognosis of the disease depend on the functional status of the kidneys. This context requires conducting a study aimed at investigating renal dysfunction in patients with acute leukemia after HSCT using the data obtained by studying the renal biomarkers - β_2 microglobulin in combination with glomerular filtration rate. We believe that this research will supplement the data on the development of renal disorders after HSCT, promoting searching for new methods for diagnosing kidney dysfunction.

Aim

The aim of this research is to study β_2 microglobulin and glomerular filtration rate in patients with acute leukemia who have undergone HSCT.

Materials and Methods

During the period from November 2020 to August 2022, a prospective study has been conducted at the National Research Oncology Center in Astana, Kazakhstan. The study has observed a group of patients with acute lymphoblastic leukemia and acute myeloid leukemia who have undergone hematopoietic stem cell transplantation.

Entry criteria

The research participants are patients with acute lymphoblastic leukemia and acute myeloid leukemia in remission. The study includes patients aged 18 years and older with preserved renal function.

The list of the exclusionary criteria includes: i) severe concomitant pathology: severe cardiovascular pathology (congestive cardiac failure, unstable angina, cardiac rhythm and conduction disorders, heart attack), hepatic impairment caused by both acute viral hepatitis and acute toxic hepatitis (serum bilirubin concentration level increased by more than 15 norms; an increase in ALT and AST activity by more than 3 norms; prothrombin index - less than 70%), decompensated diabetes mellitus; ii) severe uncontrolled infectious complications: sepsis (antibiotic-resistant fever over 38C, septicopyemia foci, hemodynamic instability); iii) life-threatening bleeding (gastrointestinal, uterine, intracerebral hemorrhage); iv) high level of PRO-BNP (exceeding 250 pg/mL); v) clinical death in anamnesis and post resuscitation disease; vi) severe mental disorders; vii) high patients' overtreatment that does not comply with diagnostic and treatment protocols.

The patients were diagnosed with acute leukemia based on the data obtained after performing a general blood test (leukoformula, reticulocytes, platelets), coagulation testing (partial thromboplastin time, thrombin clotting time, fibrinogen, D-dimer), bone marrow examination: cytological examination, cytochemical examination of blast cells (myeloperoxidase, glycogen, solvent black), immunophenotyping on a flow cytofluorimeter (HLA-DR, TdT, CD10, CD19, CD20, CD22, cytIgM, sIgM, CD1a, CD2, CD3, CD4, CD5, CD7, TCRa/β, TCRy/δ), a standard cytogenetic study and molecular genetic study by FISH (BCR/ABL, MLL), as well as analysis of cerebrospinal fluid.

The patients were examined by hematologists and nephrologists immediately after their admission. Complaints, anamnestic data, and objective examination were carried out when examining patients. The cytogenetic subgroups of acute lymphoblastic leukemia were determined according to the FAB classification. The immunological subgroups were determined according to the immunophenotypic classification of EGIL, 1995. The classification of acute myeloblastic leukemia was

determined by using phenotypic and cytochemical characteristics pointed in the classification of FAB, 1991.

Chemotherapy procedures have been performed in accordance with the clinical protocol for the diagnosis and treatment of 'Acute Lymphoblastic Leukemia in Adults' (09.07.2015) and 'Acute Myeloid Leukemia in Adults' (11.01.2019) approved by the Ministry of Healthcare of the Republic of Kazakhstan.[27]

All patients with a high risk of recurrence have undergone HSCT, provided that remission is achieved after the first consolidation treatment. Patients with 100% compatible donors in the HLA system have undergone allogeneic HSCT. Patients with 50 to 99% compatible donors in the HLA system have undergone haploidentical hematopoietic stem cell transplantation.

On the day of HSCT, all patients received a hematopoietic stem cell transfusion dosed depending on their weight, with the conditioning regimen preliminarily involved –7, –5 days before HSCT.

Neutrophilic engraftment assessment has been performed with an increase of the neutrophils level by more than 0.5 thousand/μL, the platelets level by more than 50 thousand/μL and the leukocytes level by more than 1.0 thousand/μL for three consecutive days after performing the related transplantation.

The protocol for managing patients after performing allogeneic and haploidentical stem cells transplantation management protocol is identical, having no differences in duration or in dosage of drugs. After HSCT, all the patients have undergone treatment procedures intended for preventing graft *vs* host disease (GvHD). The treatment has involved an immunosuppressive therapy introducing cyclosporine (CsA) and tacrolimus (Tx) drugs. The loading dose of CsA was administered intravenously from –1 day at a dose of 2.5 mg/kg two times per day. Starting from +4 day, the dose was reduced to 1.5 mg/kg two times per day. The initial dose of Tx was 0.03 mg/kg per day. Further on, the CsA/Tx dose was adjusted depending on the level of its concentration in the patients' blood. If possible, the oral administration of the drugs was implemented on +14 day (in the absence of acute GvHD symptoms with intestinal damage, *etc*.), at a dose of 5 mg/kg two times per day.

In order to assess the functional status of the kidneys, all patients underwent the determination of creatinine, urea, albumin, total protein, uric acid, alkaline phosphatase with the calculation of glomerular filtration rate in accordance with the CKD-EPI formula.

All participants were included in the study after signing an informed consent. All methods and experimental protocols of this study followed the relevant guidelines and standard operating procedures approved by the Ministry of Healthcare of the Republic of Kazakhstan. The study complies with the generally accepted ethical principles of clinical trials, which are regulated by the GCP standard and legal acts of the Republic of Kazakhstan. The study was carried out in accordance with the principles stated in the Declaration of Helsinki, as well as the Constitution of the Republic of Kazakhstan, the Code of the Republic of Kazakhstan 'On the health of the people and the healthcare system' dated 2009.

Collection of material

To study the β_2 microglobulin kidney biomarker, urine material was prospectively collected in sterile disposable sealed vacuum tubes displaying a barcode and patient identification number. Collection of first void urine was carried out from 7:00 a.m. to 9:00 p.m. within 10 days after HSCT. Data evaluation was carried out within 12 hours after collecting materials at a temperature of 2-8°C. The study was conducted using a clinical chemistry analyzer manufactured by Mindray (China) with calibration of reagents for urine analysis. The selection of reagents for the determination of β_2 microglobulin was based on the latex immunoturbidimetric method. The concentration of β_2 microglobulin in urine was determined by measuring the engulfment of the latex immunocomplex coated with antibodies to β_2 in the material with an analytical sensitivity of 99.7%. The normal level β_2 microglobulin concentration was <0.3 mg/L.

Serum creatinine sampling was additionally carried out within 10 days after HSCT. Glomerular filtration rate was subsequently calculated using the CKD-EPI formula.[28]

Statistical analysis

The obtained data was statistically processed using the Microsoft Excel program and the IBM SPSS Statistics Ver. 26 software (SPSS Inc., Chicago, IL, USA).

Results

A total of 41 patients with acute leukemia (hematopoietic stem cell transplantation recipients) participated in the study. The patients' average age was 36 years (min: 20 years old; max: 60 years old). The list of the participants included 20 (48.8%) female patients and 21 (51.2%) male patients. The number of patients with acute lymphoblastic leukemia was 36.6% (15 patients). The number of patients with acute myeloid leukemia was 63.4% (26 patients). The process of the patients' distribution by transplantation type showed that 20 patients (48.8%) underwent allogeneic HSCT, and 21 patients (51.2%) underwent haploidentical HSCT. Lethal outcome was stated in 17.1% (7 patients) of the studied cases (Table 1).

In the following, combined β_2-microglobulin and glomerular filtration rate data have been provided, as well as associative relation statistics data obtained by

the statistic test 'Fisher's Exact Test'. Table 2 presents all analyzed HSCT cases and separately provides data on allogeneic and haploidentical hematopoietic stem cell transplantation cases.

The results of the analysis revealed a statistically significant relationship between the level of β_2-microglobulin in the urine and the level of glomerular filtration rate ($P \leq 0.001$). In addition, patients with increased levels of β_2-microglobulin were 28.9 times more exposed to having reduced glomerular filtration rates compared to patients with normal levels of β_2 microglobulin.

The observation of the patients who have undergone allogeneic HSCT (n=21) did not reveal any statistically significant relation between the level of β_2-microglobulin and the level of glomerular filtration rate (P=0.053). On the contrary, the Haploidentical HSCT group of patients (n=21) demonstrated the association between β_2-microglobulin levels and glomerular filtration rate (P=0.010). The data are presented in Table 2.

In addition to determining the associative relation, a sensitivity-specificity graph was plotted (Figure 1). The graph presented a curve for the values of β_2-microglobulin in patients with acute leukemia who have undergone hematopoietic stem cells transplantation. In relation to reduced glomerular filtration rate (≤60 mL/min/m^2), the curve is above the reference line, in a middle position. This fact indicates acceptable diagnostic properties. Also, the study estimated the area under the ROC curve. According to the obtained results, the estimated area characterizing the diagnostic accuracy of β_2-microglobulin was 0.784 (95% CI 0.638-0.931), the latter value corresponding to the good quality of the prognostic model.

Discussion

The study investigated the kidney function in 41 patients with acute leukemia who underwent HSCT. It is

Table 1. Distribution of patients in the study, considering the type of hematopoietic stem cell transplantation.

	All cases of transplantation (n=41)	Type of transplantation	
		Allogeneic HSCT (n=21)	Haploidentical HSCT (n=20)
Gender			
Female	20 (48.8%)	10 (47.6%)	10 (50.0%)
Male	21 (51.2%)	11 (52.4%)	10 (50.0%)
Type of leukemia			
OLL	15 (36.6%)	7 (33.3%)	8 (40.0%)
OML	26 (63.4%)	14 (66.7%)	12 (60.0%)
The level of β_2-microglobulin			
B2M: >0.3 mg/L	19 (46.3%)	6 (28.6%)	13 (65.0%)
B2M: ≤0.3 mg/L	22 (53.7%)	15 (71.4%)	7 (35.0%)
Glomerular filtration rate			
≤60 mL/min	12 (29.3%)	4 (19.0%)	8 (40.0%)
>60 mL/min	29 (70.7%)	17 (81.0%)	12 (60.0%)
Outcome			
Fatal outcome	7 (17.1%)	3 (14.3%)	4 (20.0%)
Survivors	34 (82.9%)	18 (85.7%)	16 (80.0%)

HSCT, hematopoietic stem cell transplantation; OLL, acute lymphoblastic leukemia; OML, acute myeloblastic leukemia; B2M, β2 microglobulin.

Table 2. Compared data on the level of β_2-microglobulin with data on the glomerular filtration rate, and the results of association statistics.

Level β_2 microglobulin	Glomerular filtration rate		Statistics
	≤60 mL/min	>60 mL/min	Fisher's exact test
All HSCT (n=41)			
B2M: >0.3 mg/L	11	8	Fisher's exact test=0.0003,
B2M: ≤0.3 mg/L	1	21	P≤0.001
Allo HSCT (n=21)			
B2M: >0.3 mg/L	3	3	Fisher's exact test=0.053,
B2M: ≤0.3 mg/L	1	14	P=0.053
Haplo HSCT (n=20)			
B2M: >0.3 mg/L	8	5	Fisher's exact test=0.015,
B2M: ≤0.3 mg/L	0	7	P=0.010

HSCT, hematopoietic stem cell transplantation; B2M, β2 microglobulin.

considered that patients with acute leukemia may have reduced kidney function after HSCT. Based on the obtained data, it was revealed that there exists an associative relation between the level of β_2 microglobulin and glomerular filtration rate. This relation indicates impaired renal function. The obtained results are similar to the results of other foreign research studying the role of β_2 microglobulin and glomerular filtration rate.[29,30]

The world literature resources introduce research aimed at studying kidney complications after HSCT and its association with patients' survival. According to the data obtained from a US meta-study including 36 incidence studies, the incidence of kidney damage among patients undergoing HSCT is high and associated with the increased short-term and long-term mortality of patients.[31]

It is known that the determination of glomerular filtration rate is an available method for determining the functional state of the kidneys in HSCT recipients. Moreover, some authors believe that using glomerular filtration rate calculations as a decrease marker of the functional state of the kidneys can lead to biased and inaccurate evaluations. In this way, some patients who have undergone HSCT may suffer from protein-energy deficiency, which subsequently may lead to a change in patients' muscle mass and, accordingly, reduced production of creatinine. In addition, the calculation of glomerular filtration rate based on the results of the analysis of creatinine in serum can only reveal an already existing kidney damage, showing that the pathogenetic process of kidney damage has already started.[32]

In the study, it has been found that the association of the changes in the level of β_2 microglobulin and glomerular filtration rate prevailed in patients who had undergone haploidentical HSCT, compared with the group of patients who had undergone allogeneic HSCT. Thus, the authors of the conducted studies believe that the issue of organ damage mainly arises during haploidentical HSCT, with this observation revealed in this study.[33-35] The results suggest that haploidentical HSCT patients' kidneys glomerular filtration rate decreases faster compared to those patients who have undergone allogeneic HSCT.

The high urinary β_2 microglobulin level has been detected noninvasively. This data has been useful for assessing renal function in HSCT recipients. We suppose that the presence β_2 microglobulin may indicate early damage to the renal tubules, which has also been studied by other authors. Some scientists believe that an increased β_2 microglobulin level is caused by the damage to the structures of the kidneys, namely proximal kidney tubules.[36-39] At the same time, we assume that the obtained results could be influenced by the fact that those patients who had undergone HSCT received a preventive therapy against GvHD with immunosuppressive drugs, which could have had nephrotoxic effects on the kidney function.

In addition, according to a list of literary sources, there exists evidence of studying β_2 microglobulin for non-renal cases. The study of β_2-microglobulin was previously conducted by some authors who considered it a marker of hematological diseases, which predicted low survival rates of patients with acute leukemia.[40,41]

Based on the obtained data, we propose that the determination of the level of β_2 microglobulin with a threshold level of 0.3 mg/L in patients who have undergone HSCT can be used as a diagnostic marker of the functional status of the kidneys and assist in determining early kidney damage. However, we suppose that it is necessary to conduct longer studies of β_2 microglob-

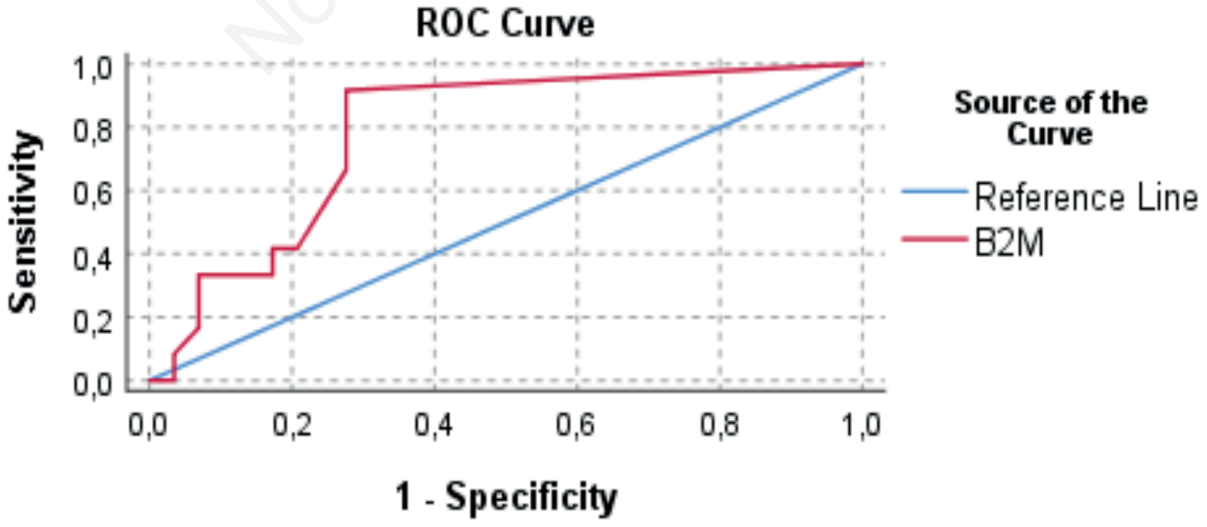

Figure 1. ROC-curve displaying diagnostic ability of the logistic regression model for verification of reduced kidney function (low glomerular filtration rate, ≤60 mL/min/m^2). B2M, β2 microglobulin.

ulin levels aimed at rationalizing the detection of reduced kidney function.

The opportunities of the study have been limited by the low number of patients. Only few patients have met the entry criteria of the study. In general, the available data provided for obtaining statistically significant differences and describing some general results based on the obtained data.

Conclusions

Studying kidney complications in patients with acute leukemia after HSCT is important and aimed at maintaining patients' clinical and hematological remission and increasing the life expectancy of patients after HSCT. It has been discovered that β_2 microglobulin is a sensitive method of analyzing renal function, with the β_2 microglobulin threshold level not exceeding 0.3 mg/L. Complex diagnostics of kidney function in HSCT recipients has given the opportunity to identify the relationship between increased β_2 microglobulin levels and decreased glomerular filtration rate, confirming β_2 microglobulin as a biomarker of renal disorders. There exists a need for conducting large-scale prospective research intended for profound β_2 microglobulin studies.

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