Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Apr 14; 10(B):937-943.
https://doi.org/10.3889/oamjms.2022.8847
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Nephrology*

Evaluation of Kidneys' Functional State in Acute Lymphoblastic Leukemia Patients Following Hematopoietic Stem Cell Transplantation

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Edited by: Ksenija Bogoeva-Kostovska
Citation: Murzakhmetova A, Kemaykin V, Kuttymuratov A, Ainabay A, Meiramova A, Tursynbet Y, Ainabekova B. Evaluation of kidneys' functional state in acute lymphoblastic leukemia patients following hematopoietic stem cell transplantation. Open Access Maced J Med Sci. 2022 Apr 14; 10(B):937-943. https://doi.org/10.3889/oamjms.2022-8847
Keywords: Hematopoietic stem cell transplantation; Bone marrow transplantation; Acute lymphoblastic leukemia; Renal failure; Meta-analysis; Systematic review; Risk factors; Glomerular filtration rate; Complications
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Received: 01-Feb-2022
Revised: 22-Mar-2022
Accepted: 04-Apr-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Hematopoietic Stem Cell Transplantation (HSCT) has recently been a widely used method of therapy in various fields of current medicine, particularly in hematology.Some patients develop renal disorders following HSCT.

AIM: This study aims to evaluate the dynamics of changes in the functional state of the kidneys in patients with ALL after HSCT.

METHODS: In the period from 2015 to 2021, for the first time in Kazakhstan, patients with acute lymphoblastic leukemia (ALL) who underwent allogeneic and haploidentical HSCT were prospectively examined.

RESULTS: We determined that the greatest decrease in glomerular filtration rate occurred in the group of patients who underwent haploidentical bone marrow transplantation. Moreover, we believe that our results are related to known contributing risk factors, such as the type of performed transplantation and the duration of taking medications for the prevention of graft versus host disease. Our results also indicate that the lethal outcome in the group with haploidentical HSCT in the studied patients with ALL was greater than in the group with allogeneic HSCT.

CONCLUSION: In conclusion, a decrease in kidney function in patients who have survived HSCT is probably a common complication; however, further prospective studies are required to confirm these results to develop additional algorithms for the treatment and prevention of renal disorders in patients with acute leukemia after HSCT.

Introduction

There have been significant achievements in the treatment of acute lymphoblastic leukemia (ALL) in adult patients over the past decades [1]. At the same time, the results of ALL treatment directly depend not only on the chemotherapeutic protocol but also on the conditions and opportunities for conducting accompanying therapy and performing hematopoietic stem cell transplantation (HSCT). HSCT has recently been a widely used method of therapy in various fields of current medicine, particularly in hematology [2], [3], [4]. There has been a 2-3-fold increase in HSCT performed in 655 centers from 48 countries over the past 10 years [5]. According to the European Group for Blood and Marrow Transplantation, 4200 HSCTs were performed in 1990, 30,000 in 2010, and in 2013 the number of HSCTs reached about 1 million [6], [7].

In Kazakhstan, HSCT for patients with hemoblastosis has been carried out since 2010 at the National Scientific Center of Oncology and Transplantology, by 2021, about 500 HCTs have been performed. As a result of chemotherapy and particularly the use of high dosages during the preparation for transplantation, HSCT recipients have to face a number of side effects and complications affecting the course and outcome of the underlying disease [8], [9], [10], [11], [12]. The main group of complications arising after HSCT includes the graft versus host disease (GvHD) [13], [14], [15], [16], infectious complications [17], [18], organ dysfunction from the hepatic [19], [20], cardiovascular [21], [22] and pulmonary systems [23]. But, among the complications that occur after HCT, renal disorders remain not fully understood. There are isolated studies in the world describing cases of kidney damage after HSCT with the development of Acute Kidney Injury, nephrotic syndrome, chronic kidney disease (CKD) [24], [25], [26], [27], [28], [29], [30]. The

main method of investigating the determination of renal dysfunction is the calculation of the glomerular filtration rate (GFR), which allows to evaluate the degree of kidney damage [31], [32]. Taking into consideration all data above, we conducted a study to assess the functional state of the kidneys in patients with acute leukemia who underwent HSCT.

The aim

To evaluate the dynamics of changes in the functional state of the kidneys in patients with ALL after HSCT.

Materials and Methods

The study was conducted at the National Scientific Cancer Center of the Ministry of Health of the Republic of Kazakhstan (Nur-Sultan) in the period from 2015 to 2021. Patients with ALL who underwent allogeneic and haploidentical HSCT were recruited. ALL was established on the basis of characteristic changes in the general blood test (leukoformula, reticulocytes, platelets), bone marrow examination: cytological examination, cytochemical examination of blast cells (myeloperoxidase, glycogen, α-naphthylesterase, solvent black), immunophenotyping on a flow cytofluorimeter (human leukocyte antigen [HLA]-DR, TdT, CD10, CD19, CD20, CD22, cytIgM, SIGMA, CD1a, CD2, CD3, CD4, CD5, CD7, TCRa/β, TCRy/δ), and based on a standard cytogenetic study and molecular genetic study by FISH (BCR/ABL, MLL), as well as analysis of cerebrospinal fluid.

The inclusion criteria were patients with ALL in remission with a preserved GFR before bone marrow transplantation (BMT) at the age of 18 years. The exclusion criteria were: (a) Severe concomitant pathology: severe cardiovascular pathology (congestive heart failure, unstable angina, rhythm and conduction disorders, heart attack), liver failure due to acute hepatitis, both viral and toxic (elevation of serum bilirubin concentration more than 15 norms, increase of alanine aminotransferase and aspartate aminotransferase activity more than 3 norms, decrease of prothrombin index <70%), renal insufficiency (elevation of serum creatinine concentration more than 0.2 mmol/l), decompensated diabetes mellitus; (b) severe uncontrolled infectious complications: sepsis (antibiotic-resistant fever over 38C, septico-pyemic foci, hemodynamic instability); (c) life-threatening bleeding (gastrointestinal, uterine, cerebral hemorrhage); (d) high level of PRO-BNP (more than 250 pg/ml); (e) clinical death in anamnesis and post-resuscitation illness; (f) severe mental disorders; (g) high patients' overtreatment, that does not comply with diagnostic and treatment protocols. The study was conducted with the approval of the local ethics committee: NJSC "Astana Medical University" in compliance with the principles of ethical standards in accordance with the Helsinki Declaration.

The examination of patients included the collection of patient complaints, clinical and anamnestic data, and an objective examination. Cytogenetic subgroups of ALL were determined according to the classification of the World Health Organization, and immunological subgroups according to the immunophenotypic classification European Group for Immunophenotypic Characterization of Leukemias, 1995. To assess the functional state of the kidneys, all patients underwent a laboratory examination, which included determination the level of hemoglobin, leukocytes, albumin, total protein, uric acid, alkaline phosphatase, creatinine and GFR calculation, using CKD-Epidemiology Collaboration (CKD-EPI) formula. The clinical and anamnestic characteristics of patients are presented in Table 1.

Table 1: Clinical and anamnestic characteristics of all patients under the study

Variables	n (%)/mean (SD)
Age of patients	31.3 (1.1)
Ethnicity	
Kazakh ethnic group	44 (86.3)
Slavic ethnic group	7 (13.7)
Presence of risk factors	21 (41.2)
Gender	
Female	27 (52.9)
Male	24 (47.1)
B-I (pro-B)	12 (25)
B-II (common B)	22 (45.8)
B-III (pre-B)	6 (12.5)
T-I (pro-T)	4 (8.3)
T-II (pre-T)	2 (4.2)
T-III (cortical T)	2 (4.2)

SD: Standard deviation.

Patients with 100% compatible donors by the HLA system underwent allogeneic HSCT, patients with 50–99% compatible donors by the HLA system underwent haploidentical stem cell transplantation. The transfusion of a hematopoietic stem cell suspension on day zero, according to the patient's weight, with the preliminary introduction of a conditioning scheme was carried out to all patients. Chemotherapy was carried out according to the approved clinical protocol of diagnosis and treatment by the Ministry of Health of the Republic of Kazakhstan [33] «ALL in adults» from 09.07.2015. In the treatment of ALL, the protocol ALL-2013Kz was used. All patients were pre-treated after the diagnosis of ALL establishment. Allogenic HSCT was carried out for patients at high risk of relapse, providing that the remission after the first course of consolidation with a related or compatible unrelated donor was achieved. If after the completion of phase I induction remission is not achieved (21st day of the course), the patient is classified as a high-risk group, treatment is carried out under programs for resistant forms (FLAG± Ida, HyperCVAD, All-Rez BFM 2002). If remission is achieved and there is a donor, allogenic BMT was performed. Upon detection of t (9; 22)/BCR-ABL, patients are transferred to treatment by the protocol

using tyrosine kinase inhibitors, i.e., Ph+All 2013 Kz protocol. Patients from the standard risk group and patients from the high-risk group were administered five courses of the consolidation of remission and a further for 2 years of maintenance therapy. Recommendations from international protocols such as GMALL 07/2003 (German Multicenter Study Group for Adult ALL) and OLL-2009 (Russia) were used and modernized in the development of the ALL-2013Kz protocol.

Neutrophilic engraftment assessment was performed with in an increase of leukocytes level by more than 1.0 thousand/μl for three consecutive days after transplantation. All patients in the post-transplant period underwent preventive treatment GvHD with the introduction of cyclosporine and tacrolimus. The initial administration of cyclosporine (CsA) was injected from-1 day at a dose of 2.5 mg/kg × 2 times per day with further dose reduction from +4 day to 1.5 mg/kg × 2 times per day. The initial dose of tacrolimus was (Tx) 0.03 mg/kg/day. The patients` after allogeneic and haploidentical stem cells transplantation management protocol was identical and had no differences either in duration or in dosage of drugs. As a result of the medical records analysis, patients who underwent BMT were divided into two groups. Further observation and data processing was carried out, taking into consideration the patients' distribution by transplantation type. The first group consisted of patients with allogeneic HSCT in the number of 26 people, while the second group included patients who underwent haploidentical HSCT in the number of 25 people. All patients were re-examined 1 and 2 years after HSCT in purpose to assess the underlying disease condition and kidney function. Hemoglobin, leukocytes, albumin, total protein, uric acid, alkaline phosphatase, creatinine were determined in dynamics, within the specified time frame, with the calculation of GFR, according to the CKD-EPI formula.

Statistical analysis

Statistical data processing was performed using the IBM SPSS Statistics software package (Version 20, SPSS Inc., Chicago, Illinois,USA).

Results

A comparative analysis of the study groups showed that the age characteristics of the first and second patients' groups did not have statistically significant differences, and while in the group with allogeneic transplantation the age of patients was 32.2 years standard deviation (SD) = 1.7, in the group with haploidentical transplantation it was equal to 30.3 years SD = 1.5 (p = 0.445). The gender distribution among the groups also did not differ statistically, so the men-to-women ratio in the first group was 57.7% (95% confidence interval [CI] 38.9–24.5)/42.3% (95% CI 25.5–61.1), and in the second group 48% (95%CI 30–66.5)/52% (95% CI 33.5–70) (p = 0.488). The ratio by ethnicity of the patients under the study did not statistically differ (p = 0.202).

Comparative analysis of immunophenotypic subgroups of ALL also showed the absence of statistically significant differences (p = 0.996), the distribution of which is shown in Figure 1.

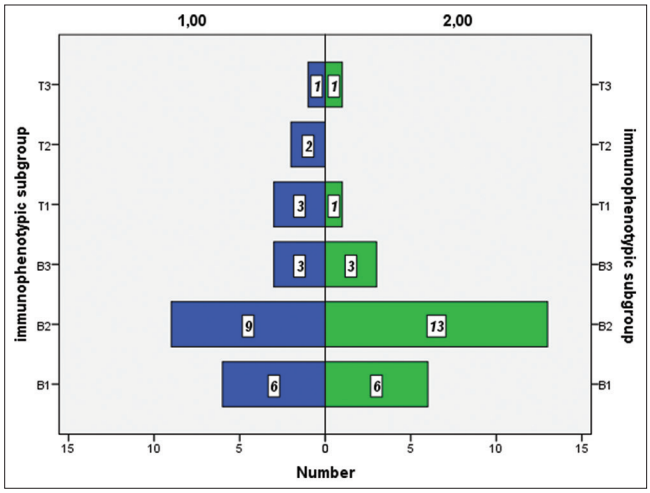

Figure 1: Distribution of both groups' patients by acute lymphoblastic leukemia immunophenotypic subgroups

There were no statistically significant differences in the study of the frequency of complications of the underlying disease before the HSCT, and the data are presented in Table 2.

Table 2: The frequency of the underlying disease complications prior the hematopoietic stem cell transplantation

Variable	AlloHSCT	HaploHSCT (n = 25)			Significance level
	(n = 26), n (%)	95% CI	n (%)	95% CI	
Absence of remission prior to HSCT	4 (15.4)	6.1–33.5	6 (24)	11.5–43.4	0.439
Recurrence prior to HSCT	4 (15.4)	6.1–33.5	2 (8)	2.2–25	0.413
Chemoresistance	1 (3.8)	0.7–18.9	1 (4)	0.7–19.5	0.977
Hyperleukocytosis	2 (7.7)	2.1–24.1	1 (4)	0.7–19.5	0.575
Neuroleukosis	5 (19.2)	8.5–37.9	2 (8)	2.2–25	0.244

HSCT: Hematopoietic stem cell transplantation, CI: Confidence interval, AlloHSCT: Allogeneic HSCT, HaploHSCT: Haploidentical HSCT.

Analysis of general clinical laboratory data in both groups showed that after high-dose chemotherapy in all patients with ALL, the blood recovery pattern lasted on average from 3 weeks to 2 months. Meanwhile, the clinical-functional condition of the kidneys after chemotherapy in this period did not have significant changes. Consequently, blood analysis, urine analysis, and the GFR filtration did not show any significant change. The instrumental examination of kidney structural changes of the patients under the study in this period did not have any changes.

Next, a comparative analysis of the two groups according to the Mann–Whitney criterion at different stages of examination was performed, which showed that the laboratory parameters of the study patients did

not statistically differ either before the intervention, or after a year, or after 2 years, respectively. The data are given in Table 3.

Table 3: Dynamics of laboratory parameters in both groups prior hematopoietic stem cell transplantation, 1 year later, 2 years after transplantation

Variables	AlloHSCT (n = 26)		HaploHSCT (n = 25)		Significance level
	Me	Q1–Q3	Me	Q1–Q3	
Prior the HSCT performance					
Hb (g/l)	91	76–120	80	68–104	0.429
Leukocyte (×10^9 cells/l)	6.7	3.01–61.8	3.4	1.57–62.9	0.749
Albumin (g/l)	40.5	36–44.2	41	34.6–43.9	0.280
Total protein (g/l)	67	59.1–70.2	66	55.1–70.1	0.134
Uric acid (μmol/l)	327.7	267–384	267	207–400.5	0.488
Alkaline phosphatase (units/l)	107	86–145	120	70.5–161	0.800
Creatinine (mkmol/l)	63	49–79.1	57.4	44–81.5	0.295
GFR (ml/min/1.73 m^2)	127	94–149	110,5	103.5–163	0.472
1 year after the HSCT performance					
Hb (g/l)	115.5	104–132	107.5	92–125.7	0.358
Leukocyte (×10^9 cells/l)	5.1	3.49–6.3	5.42	3.87–7.35	0.367
Albumin (g/l)	47.2	43.3–49.9	39.9	33.1–47.7	0.092
Total protein (g/l)	74.9	70–78	66.1	55.5–69.4	0.007
Uric acid (μmol/l)	261	182.5–342	265	197.5–295	0.516
Alkaline phosphatase (units/l)	108.5	87.2–179	90.5	74.7–134	0.292
Creatinine (mkmol/l)	64	50–79.6	57	48.7–99.6	0.334
GFR (ml/min/1.73 m^2)	120	103.5–153.7	128.5	80.2–155	0.262
2 years after the HSCT performance					
Hb (g/l)	118	109–135	128	125.5–135	0.478
Leukocyte (×10^9 cells/l)	3.7	2.9–4.4	5.2	5.4–6.4	0.250
Albumin (g/l)	47.2	41–49	47.8	44.9–50.7	0.512
Total protein (g/l)	74.5	67–76.5	73.2	65–79.8	0.341
Uric acid (μmol/l)	309.5	190–382	335	290–387.5	0.123
Alkaline phosphatase (units/l)	85	62–90	108	92–116	0.540
Creatinine (mkmol/l)	68	58.8–87.3	98	77–108	0.326
GFR (ml/min/1.73 m^2)	111	88–125	82	73–116.5	0.370
3 years after the HSCT performance					
Hb (g/l)	148		91		Not subject to comparison due to the small number of cases
Leukocyte (×10^9 cells/l)	5.95		3.79		
Albumin (g/l)	51.7		38.14		
Total protein (g/l)	77.3		67		
Uric acid (μmol/l)	335.4		296		
Alkaline phosphatase (units/l)	94		100		
Creatinine (mkmol/l)	69		80		
GFR (ml/min/1.73 m^2)	130		102		

HSCT: Hematopoietic stem cell transplantation, AlloHSCT: Allogeneic HSCT, HaploHSCT: Haploidentical HSCT, Hb: Hemoglobin, GFR: Glomerular filtration rate.

However, a comparative analysis of the dependent variables of the kidneys' functional state of in dynamics showed a statistically significant decrease in the GFR level among patients with haploidentical HSCT, and a tendency to increase of plasma creatinine levels in these patients over time, the results are presented in Table 4.

Table 4: Comparative analysis of the first group laboratory data according to the Friedman criterion

Variables	Comparative analysis of the laboratory data of patients with AlloHSCT in dynamics		Comparative analysis of the laboratory data of patients with HaploHSCT in dynamics	
	χ^2	p	χ^2	p
Hb (g/l)	12.9	0.002	1.4	0.497
Leukocyte (×10^9 cells/l)	0.154	0.926	2.6	0.273
Albumin (g/l)	5.429	0.066	1.6	0.449
Total protein (g/l)	3.677	0.159	3.2	0.202
Uric acid (μmol/l)	2.400	0.301	1,0	0.607
Alkaline phosphatase (units/l)	2.571	0.276	1.0	0.607
Creatinine (mkmol/l)	3.571	0.312	5.216	0.074
GFR (ml/min/1.73 m^2)	0.000	1.0	7.051	0.032

AlloHSCT: Allogeneic hematopoietic stem cell transplantation, HaploHSCT: Haploidentical hematopoietic stem cell transplantation, Hb: Hemoglobin, GFR: Glomerular filtration rate.

A comparative analysis on the frequency of complications after HSCT, where the proportion of graft rejection cases, the recurrence' development and graft-versus-host reactions, as well as the development of the frequency of such an endpoint as a lethal outcome, were evaluated, was also carried out, the data are presented in Table 5.

Table 5: The frequency of complications of the underlying disease following hematopoietic stem cell transplantation

Variable	The first group (n = 26)		The second group (n = 25)		Significance level
	n (%)	95% CI	n (%)	95% CI	
Engraftment	1 (3.8)	0.7–18.9	2 (8)	2.2–25	0.529
Recurrence after HSCT	5 (19.2)	8.5–37.9	4 (16)	6.4–34.7	0.762
Preventive graft versus host therapy conducting	14 (53.8)	35.5–71.2	21 (84)	65.3–93.6	χ^2 = 5.382, df = 1 P = 0.02
Graft versus host reaction	11 (42.3)	25.5–61.1	13 (52)	33.5–70	0.488
Lethal outcome	10 (38.5)	22.4–57.5	13 (52)	33.5–70	0.331

HSCT: Hematopoietic stem cell transplantation, CI: Confidence interval.

Among the studied two groups of patients after HSCT, there were only nine patients with relapse of ALL. The average GFR in these patients before HSCT was 116 ml/min/1.73 m^2. At the same time, GFR after 1 year in patients with relapse was reduced to 87 ml/min/1.73 m^2 and after 2 years decreased to 71.5 ml/min/1.73 m^2.

Considering the rather high frequency of deaths, we conducted an analysis of the survival of censored data, which showed a tendency to a higher frequency of deaths in the second study group, Figure 2.

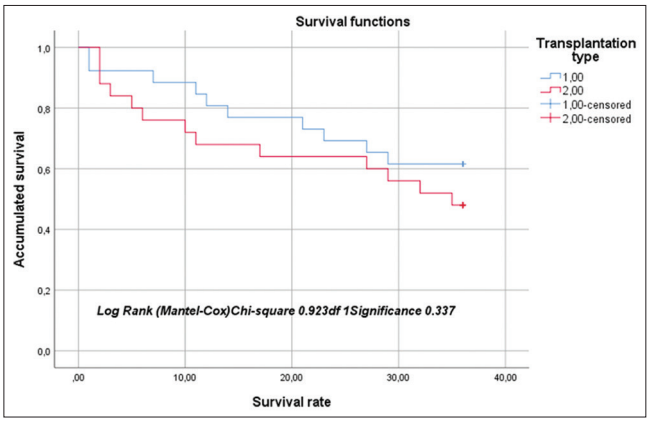

Figure 2: Survival of patients after allogeneic and haploidentical Hematopoietic Stem Cell Transplantation

Discussion

In this study, we investigated kidney function in 51 patients with ALL. Evaluation of the kidneys functional state was carried out before BMT and after 1 and 2 years. Based on the results of the obtained data, we assume that the patients' kidneys functional state depend on the type of HSCT performed. We determined that the greatest decrease in the GFR occurs during haploidentical HSCT. The obtained results, firstly, make it possible to assume that in patients who underwent haploidentical BMT, the GFR of the kidneys decreases faster in comparison with patients who underwent allogeneic transplantation. According to a systematic review by Ellis *et al*., renal disorders developed in a

significant proportion of patients whose survival was more than 100 days after HSCT [34]. These research results are probably related to the presence of risk factors for the after transplantation renal disorders development, which, according to many authors, are: acute or chronic graft versus host reaction, type of transplantation performed, gender, age of the patient, initial kidneys functional state, duration of taking medications for the GVHD prevention (prograf, tacrolimus) and treatment of GVHD (GCS, immunosuppressive therapy, etc.) [35]. In addition, according to studies by Nicole Santoro *et al*., it is known that, in HaploHSCT recipients, the incidence of GVHD of various organs is significantly higher compared to AlloHSCT, which coincided with the data of our study [36], [37], [38], [39], [40].

HaploHSCT recipients showed a tendency to decrease the total protein in the blood during the 1st year after BMT with its gradual normalization. This was probably due to the nutritional status violation, as result of the prevention of GVHD. The obtained results are comparable to the previously known findings of other foreign studies, where protein-energy deficiency was studied in conditions of HSCT [41].

There are studies in the world literature on the kidneys prognosis and the associated overall patients' survival. According to the data of Hingorani *et al*., the mortality of patients with acute leukemia increased as the kidneys GFR decreased, regardless of the transplantation type [42]. Whereas our results indicate that the lethal outcome in the haploidentical HSCT group of patients with ALL was greater than in the allogeneic HSCT group. One of the limitations of our study was the low number of patients, since only a few patients met the inclusion criteria for the study. In general, the absence of a larger number of participants did not allow us to give statistically significant differences; however, we described some common results based on the available data.

Conclusion

Consequently, we determined that the greatest decrease in the GFR occurred in the patients group who underwent haploidentical BMT, which makes it possible to predict a general decrease in the kidneys functional state in this category of patients. We believe that our results are related to known risk factors, such as the performed transplantation type and the duration of taking medications for the GVHD prevention. Our results also indicate that the lethal outcome in the haploidentical HSCT group in the study of patients with ALL was greater than in the allogeneic HSCT group. Our results reflect the importance of determining creatinine in blood serum, which is a standardized, affordable, and widely available research method. At the same time, further calculation of the kidneys GFR prior to transplantation and in the post-transplantation period is easily applicable in making clinical decisions in real time. The increase in the number of transplantations performed both in Kazakhstan and around the world leads to an upsurge in the burden of kidney diseases on the health system. We believe that research in the HSCT area should also be aimed at studying risk factors and at earlier detection of renal pathology to conduct the early possible intervention.

Availability of Data and Material

Data and material used during this study will be available from the corresponding author upon request.

Author Contributions

BA and VM, designed research and critically revised the paper; AO, AM and Ayagul M. performed patient recruitment and clinical and laboratory examination; AO and Assel M. performed statistical analysis; BA, AO, and Assel M. analyzed data; BA and Ayagul M. critically revised the paper; BA and TE provided key technical support; AO wrote the paper.

Informed Consent/Ethics Approval

The study was performed in accordance with the rules and principles of the Helsinki Declaration; informed consent was obtained from all participants. The study was approved by the Ethics Committee Laboratory of the National scientific center of oncology and transplantology.

References

1. Available from: https://www.wbmt.org. [Last accessed on 2021 Sep 25].
2. Niederwieser D, Baldomero H, Szer J, Gratwohl M, Aljurf M, Atsuta Y, *et al*. Hematopoietic stem cell transplantation activity worldwide in 2012 and a SWOT analysis of the Worldwide Network for Blood and Marrow Transplantation Group including the global survey. Bone Marrow Transplant. 2016;51(6):778-85. https://doi.org/10.1038/bmt.2016.18
PMid:26901703

3. DeFilipp Z, Advani AS, Bachanova V, Cassaday RD, Deangelo DJ, Kebriaei P, *et al*. Hematopoietic cell transplantation in the treatment of adult acute lymphoblastic leukemia: Updated 2019 Evidence-Based Review from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2019;25(11):2113-23. https://doi.org/10.1016/j.bbmt.2019.08.014
   PMid:31446198
4. Simpson E, Dazzi F. Bone marrow transplantation 1957-2019. Front Immunol. 2019;10:1246. https://doi.org/10.3389/fimmu.2019.01246
   PMid:31231381
5. Passweg JR, Baldomero H, Bader P, Bonini C, Duarte RF, Dufour C, *et al*. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. Bone Marrow Transplant. 2017;52(6):811-7. https://doi.org/10.1038/bmt.2017.34
   PMid:28287639
6. Chien SH, Liu YC, Liu CJ, Ko PS, Wang HY, Hsiao LT, *et al*. European Group for Blood and Marrow Transplantation score correlates with outcomes of older patients undergoing allogeneic hematopoietic stem cell transplantation. J Chin Med Assoc. 2020;83(3):238-44. https://doi.org/10.1097/JCMA.0000000000000255
   PMid:31904659
7. Pasquini MC, Wang Z, Horowitz MM, Gale RP. 2010 report from the center for international blood and marrow transplant research (CIBMTR): Current uses and outcomes of hematopoietic cell transplants for blood and bone marrow disorders. Clin Transplant 2010;87-105.
8. Sedhom R, Sedhom D, Jaimes E. Mini-review of kidney disease following hematopoietic stem cell transplant. Clin Nephrol. 2018;89(6):389-402. https://doi.org/10.5414/CN109276
   PMid:29578399
9. Kanduri SR, Kovvuru K, Cheungpasitporn W, Thongprayoon C, Bathini T, Garla V, *et al*. Kidney recovery from acute kidney injury after hematopoietic stem cell transplant: A systematic review and meta-analysis. Cureus. 2021;13(1):e12418. https://doi.org/10.7759/cureus.12418
   PMid:33659105
10. Inamoto Y, Lee SJ. Late effects of blood and marrow transplantation. Haematologica. 2017;102(4):614-25. https://doi.org/10.3324/haematol.2016.150250
    PMid:28232372
11. Mii A, Shimizu A, Yamaguchi H, Tsuruoka S. Renal complications after hematopoietic stem cell transplantation: Role of graft-versus-host disease in renal thrombotic microangiopathy. J Nippon Med Sch. 2020;87(1):7-12. https://doi.org/10.1272/jnms.JNMS.2020_87-102
    PMid:31776318
12. Wu NL, Hingorani S, Cushing-Haugen KL, Lee SJ, Chow EJ. Late kidney morbidity and mortality in hematopoietic cell transplant survivors. Transplant Cell Ther. 2021;27(5):434.e1-6. https://doi.org/10.1016/j.jtct.2021.02.013
    PMid:33775588
13. Yoshimura K, Kimura SI, Kawamura M, Kawamura S, Takeshita J, Yoshino N, *et al*. Chronic liver graft-versus-host disease in allogeneic hematopoietic stem cell transplantation recipients during tapering or after stopping calcineurin inhibitors. Int J Hematol. 2021;114(6):674-81. https://doi.org/10.1007/s12185-021-03202-x
    PMid:34378178
14. Giaccone L, Faraci DG, Butera S, Lia G, Di Vito C, Gabrielli G, *et al*. Biomarkers for acute and chronic graft versus host disease: State of the art. Expert Rev Hematol. 2021;14(1):79-96. https://doi.org/10.1080/17474086.2021.1860001
    PMid:33297779
15. Poonsombudlert K, Kewcharoen J, Prueksapraopong C, Limpruttidham N. Engraftment syndrome and acute graft-versus-host disease: A meta-analysis. Hawaii J Health Soc Welf. 2020;79(6):194-201.
    PMid:32524098
16. Piccin A, Tagnin M, Vecchiato C, Al-Khaffaf A, Beqiri L, Kaiser C, *et al*. Graft-versus-host disease (GvHD) of the tongue and of the oral cavity: A large retrospective study. Int J Hematol. 2018;108(6):615-21. https://doi.org/10.1007/s12185-018-2520-5
    PMid:30144000
17. Foord AM, Cushing-Haugen KL, Boeckh MJ, Carpenter PA, Flowers ME, Lee SJ, *et al*. Late infectious complications in hematopoietic cell transplantation survivors: a population-based study. Blood Adv. 2020;4(7):1232-41. https://doi.org/10.1182/bloodadvances.2020001470
    PMid:32227211
18. Stohs E, Kalil AC. A sepsis screening tool for hematopoietic cell transplant recipients remains elusive. Clin Infect Dis. 2021;72(7):1230-1. https://doi.org/10.1093/cid/ciaa221
    PMid:32133484
19. Xia Y, Qin H, Yang J. Hepatic veno-occlusive disease development in the hematopoietic stem cell transplantation patients: Incidence and associated risk factors, a meta-analysis. Eur J Gastroenterol Hepatol. 2021;33(6):872-84. https://doi.org/10.1097/MEG.0000000000001802
    PMid:32639417
20. Karagun BS, Akbas T, Erbey F, Sasmaz İ, Antmen B. The prophylaxis of hepatic veno-occlusive disease/sinusoidal obstruction syndrome with defibrotide after hematopoietic stem cell transplantation in children: Single center experience. J Pediatr Hematol Oncol. 2022;44(1):e35-9. https://doi.org/10.1097/MPH.0000000000002379
    PMid:34966102
21. López-Fernández T, Vadillo IS, de la Guía AL, Barbier KH. Cardiovascular issues in hematopoietic stem cell transplantation (HSCT). Curr Treat Options Oncol. 2021;22(6):51. https://doi.org/10.1007/s11864-021-00850-3
    PMid:33939030
22. Chang E, Iukuridze A, Echevarria M, Teh JB, Chanson D, Ky B, *et al*. Feasibility and acceptability of using a telehealth platform to monitor cardiovascular risk factors in hematopoietic cell transplantation survivors at risk for cardiovascular disease. Biol Blood Marrow Transplant. 2020;26(6):1233-7. https://doi.org/10.1016/j.bbmt.2020.02.027
    PMid:32171884
23. Astashchanka A, Ryan J, Lin E, Nokes B, Jamieson C, Kligerman S, *et al*. Pulmonary complications in hematopoietic stem cell transplant recipients – A clinician primer. J Clin Med. 2021;10(15):3227. https://doi.org/10.3390/jcm10153227
    PMid:34362012
24. Sakaguchi M, Nakayama K, Yamaguchi H, Mii A, Shimizu A, Inai K, *et al*. Risk factors for acute kidney injury and chronic kidney disease following allogeneic hematopoietic stem cell transplantation for hematopoietic malignancies. Acta Haematol. 2020;143(5):452-64. https://doi.org/10.1159/000504354
    PMid:31822013
25. Hingorani S. Renal complications of hematopoietic-cell transplantation. N Engl J Med. 2016;374(23):2256-67. https://doi.org/10.1056/NEJMra1404711
    PMid:27276563
26. Ando M. An overview of kidney disease following hematopoietic cell transplantation. Intern Med 2018;57(11):1503-8. https://doi.

org/10.2169/internalmedicine.9838-17

27. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. Lancet. 2017;389(10075):1238-52. https://doi.org/10.1016/S0140-6736(16)32064-5
PMid:27887750
28. Vorob'ev PA, Dvoretskiĭ LI, Iaroslavtseva GN, Ainabekova BA, Miagkov AV. O sviazi mezhdu arterial'noĭ gipertonieĭ i narusheniem deformiruemosti éritrotsitov u bol'nykh s khronicheskoĭ pochechnoĭ nedostatochnost'iu [Relation between arterial hypertension and disorder of erythrocyte deformability in patients with chronic renal failure]. Ter Arkh. 1988;60(6):65-6. Russian.
PMid:3206374
29. Shimoi T, Ando M, Munakata W, Kobayashi T, Kakihana K, Ohashi K, *et al*. The significant impact of acute kidney injury on CKD in patients who survived over 10 years after myeloablative allogeneic SCT. Bone Marrow Transplant. 2013;48(1):80-4. https://doi.org/10.1038/bmt.2012.85
PMid:22635246
30. Cohen EP, Pais P, Moulder JE. Chronic kidney disease after hematopoietic stem cell transplantation. Semin Nephrol. 2010;30(6):627-34. https://doi.org/10.1016/j.semnephrol.2010.09.010
31. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002 Feb;39 2 Suppl 1:S1-266.
PMid:11904577
32. Levey AS, Inker LA, Coresh J. GFR estimation: From physiology to public health. Am J Kidney Diseases 2014;63(5):820-34. https://doi.org/10.1053/j.ajkd.2013.12.006
33. Clinical Protocols of the Ministry of Health of the Republic of Kazakhstan. Acute Lymphoblastic Leukemia in Adults 2015. Republican Center for Health Development of the Ministry of Health of the Republic of Kazakhstan. Available from: https://www.rcrz.kz [Last accessed on 2021 Sep 25].
34. Ellis MJ, Parikh CR, Inrig JK, Kanbay M, Patel UD. Chronic kidney disease after hematopoietic cell transplantation: A systematic review [published correction appears in Am J Transplant. 2009 Apr;9(4):865. Kambay, M [corrected to Kanbay, M]]. Am J Transplant. 2008;8(11):2378-90. https://doi.org/10.1111/j.1600-6143.2008.02408.x
PMid:18925905
35. Saunders IM, Tan M, Koura D, Young R. Long-term follow-up of hematopoietic stem cell transplant survivors: A focus on screening, monitoring, and therapeutics. Pharmacotherapy. 2020;40(8):808-41. https://doi.org/10.1002/phar.2443
PMid:32652612
36. Santoro N, Ruggeri A, Labopin M, Bacigalupo A, Ciceri F, Gülbaş Z, *et al*. Unmanipulated haploidentical stem cell transplantation in adults with acute lymphoblastic leukemia: A study on behalf of the Acute Leukemia Working Party of the EBMT. J Hematol Oncol. 2017;10(1):113. https://doi.org/10.1186/s13045-017-0480-5
PMid:28558762
37. Yang B, Yu R, Cai L, Guo B, Chen H, Zhang H, *et al*. Haploidentical versus matched donor stem cell transplantation for patients with hematological malignancies: A systemic review and meta-analysis. Bone Marrow Transplant. 2019;54(1):99-122. https://doi.org/10.1038/s41409-018-0239-9
PMid:29988061
38. Meybodi MA, Cao W, Luznik L, Bashey A, Zhang X, Romee R, *et al*. HLA-haploidentical vs matched-sibling hematopoietic cell transplantation: a systematic review and meta-analysis. Blood Adv. 2019;3(17):2581-5. https://doi.org/10.1182/bloodadvances.2019000614
PMid:31484635
39. Wieduwilt MJ, Metheny L, Zhang MJ, Wang HL, Estrada-Merly N, Marks DI, *et al*. Haploidentical vs sibling, unrelated, or cord blood hematopoietic cell transplantation for acute lymphoblastic leukemia. Blood Adv. 2022;6(1):339-57. https://doi.org/10.1182/bloodadvances.2021004916
PMid:34547770
40. Rafiee M, Abbasi M, Rafieemehr H, Mirzaeian A, Barzegar M, Amiri V, *et al*. A concise review on factors influencing the hematopoietic stem cell transplantation main outcomes. Health Sci Rep. 2021;4(2):e282. https://doi.org/10.1002/hsr2.282
PMid:33977164
41. Barban JB, Simões BP, Moraes BD, *et al*. Brazilian nutritional consensus in hematopoietic stem cell transplantation: Adults. Einstein (Sao Paulo). 2020;18:AE4530. https://doi:10.31744/einstein_journal/2020AE4530
PMid:32049129
42. Hingorani S, Pao E, Stevenson P, Schoch G, Laskin BL, Gooley T, *et al*. Changes in glomerular filtration rate and impact on long-term survival among adults after hematopoietic cell transplantation: A prospective cohort study. Clin J Am Soc Nephrol. 2018;13(6):866-73. https://doi.org/10.2215/CJN.10630917.
PMid:29669818