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RESULTS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN AT THE CLINIC OF THE SCIENTIFIC CENTER OF PEDIATRICS AND PEDIATRIC SURGERY

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ABSTRACT

Relevance: *Hematopoietic stem cell transplantation (HSCT) is a method of providing highly specialized care to patients with various oncological and hematological diseases, primary immunodeficiencies, as well as other congenital and hereditary diseases affecting the hematopoietic and immune systems. In Kazakhstan, HSCT has been performed for pediatric patients since 2012 at the Scientific Center of Pediatrics and Pediatric Surgery (SCPPS, Almaty, Kazakhstan). The article presents the experience of conducting allogeneic HSCT in children with oncohematological pathology at SCPPS.*

The study aimed to *analyze the results of allo-HSCT and the possible influence of factors such as gender, conditioning regimen, donor compatibility, and status of the underlying disease at the time of HSCT on the survival rates of patients after HSCT in order to improve the treatment results and quality of life of patients with high-risk oncohematological diseases.*

Methods: *Retrospective analysis of observational data on 53 patients after HSCT, carried out at the Scientific Center of Pediatrics and Pediatric Surgery from 2012 to 2020. Patient survival was assessed according to Kaplan-Meier, and static processing was carried out using the SPSS Statistic program.*

Results: *In our study, 39.6% of patients were diagnosed with acute lymphoblastic leukemia (ALL, n=21), 28.85% of patients (n=15) with acute myeloblastic leukemia (AML), for aplastic anemia alloHSCT was performed in 20.75% of cases (n=11), in 9.46% (n=5) alloHSCT was performed for myelodysplastic syndrome (MDS), of which three patients (60%) had juvenile myelomonocytic leukemia (JMML). According to the results of the study, when performing allo-HSCT, the overall survival rate of patients with ALL after from a matched related donor was 63.6%, while when performing HSCT in the earliest stages from the onset of the disease, survival rates were significantly higher (83.3%). The effectiveness of HSCT was also influenced by treatment before transplantation and the presence of a fully matched related donor. In aplastic anemia, the time from the start of therapy is a significant factor.*

Conclusion: *HSCT is an important and necessary stage of therapy for oncological and hematological diseases of high-risk groups in the early stages and in case of relapses of diseases. When HSCT was performed in the earliest period from the onset of the disease, survival rates were significantly higher (83.3%) compared to those with HSCT performed during the 3rd remission. Also, it was shown that the success of HSCT depends on previous therapy. HSCT in children with aplastic anemia should be performed early from the onset of the disease with minimal hematological load to HSCT, which guarantees engraftment.*

Keywords: *hematopoietic stem cell transplantation, children, acute leukemia, oncohematological diseases.*

Introduction: In the past 30 years, treating pediatric patients with leukemia and other oncohematological disorders in the Republic of Kazakhstan has experienced substantial transformations. Since 1993, the protocols of international cooperative groups have been implemented throughout the country, notably including the protocol for treating acute lymphoblastic leukemia established by the German cooperative group BFM. Simultaneously, the treatment program for pediatric oncohematological diseases progressively included more sophisticated and contemporary chemotherapy methods.

The implementation of standardized chemotherapy protocols and the improvement of adjunctive therapies have enhanced the prognosis of leukemia and other oncohematological disorders in Kazakhstan, resulting in a substantial rise in pediatric survival rates. Nonetheless, despite the advancements in the treatment of acute leukemias, few patients exhibited inadequate response to conventional chemotherapy and experienced disease relapses, requiring a novel, more rigorous, intensive therapeutic intervention.

In 2012, the establishment of a hematopoietic stem cell transplantation (HSCT) department at the Scientific Center of Pediatrics and Pediatric Surgery (SCPPS) in Almaty, Kazakhstan, marked a new phase in the advancement of the children's oncohematology service in the Republic of Kazakhstan.

HSCT is a method for delivering specialized treatment to infants suffering from diverse oncological and hematological disorders, severe combined primary immunodeficiencies, and other congenital and hereditary diseases that include impairment of the hematopoietic and immune systems. Bone marrow transplantation as a therapeutic approach is advancing rapidly and is increasing-

ly employed in pediatric treatment. In the United States, more than 1,000 pediatric hematopoietic stem cell transplants have been conducted yearly during the previous decade. HSCT encompasses pre-transplant immunosuppressive and myeloablative therapies and a comprehensive array of adjunctive treatments designed to optimize safety during the post-transplant phase. The transplantation method is continually being improved to accommodate more patients, including children. This article discusses the experience of HSCT in pediatric patients with oncohematological disorders at the SCPPS.

The study aimed to analyze the results of allo-HSCT and the possible influence of factors such as gender, conditioning regimen, donor compatibility, and status of the underlying disease at the time of HSCT on the survival rates of patients after HSCT in order to improve the treatment results and quality of life of patients with high-risk oncohematological diseases.

Materials and Methods: We retrospectively analyzed observational data on 53 patients after HSCT treated at SCPPS from 2012 to 2020.

We analyzed medical records of 53 allo-HSCTs (two patients required two repeated allo-HSCTs) performed at the SCPPS clinic. The study included all patients who underwent allo-HSCT at SCPPS. The assessed factors were the patient gender and age, nosological form and period of the disease, presence of concomitant infection, duration of therapy before HSCT, donor characteristics, transplant engraftment time, complications, and overall survival. We analyzed the possible influence of such factors as gender, conditioning regimen, donor compatibility, and the status of the underlying disease at the time of HSCT on the survival rates of patients after HSCT. Today, different centers actively study the influence of the above factors on HSCT outcomes in children. The accumulation of such data can serve as a basis for developing unified diagnostic and therapeutic approaches [2].

Patient survival was assessed using the Kaplan-Meier method; statistical processing was performed using the SPSS Statistics program (IBM SPSS, USA).

Results: Allo-HSCT was performed for 53 children with various oncohematological diseases treated at the SCPPS clinic from 2012 to 2020.

Allo-HSCT was performed for the following nosologies: 21 acute lymphoblastic leukemia cases (39% of all cases); of them, 42.8% (n=9) of allo-HSCTs were performed during the 2nd remission, and 33.3% (n=7) during the 3rd remission, which, according to global data, significantly reduces the effectiveness of the treatment [3].

28.85% (n= 15) were children with acute myeloid leukemia; of them, 20% (n= 3) underwent HSCT after the FLAI protocol therapy in a state of incomplete hematologic remission, and 73.3% (n=11) underwent HSCT during the second or third remission.

Allo-HSCT was performed on 20.75% (n=11) of children with aplastic anemia. Of them, 54.5% (n=6) had a very severe form, and 45.5% (n=5) had a severe form.

In 9.46% (n=5) of cases, allo-HSCT was performed for myelodysplastic syndrome, including three patients (60%) with juvenile myelomonocytic leukemia.

In one case (1.9%), allo-HSCT was performed on a patient with primary severe combined immunodeficiency (Table 1).

Table 1 – Structure of diseases for which allogeneic hematopoietic stem cell transplantation was performed

Diagnosis	No. of patients, n (%)	Nosological form/period of the disease, n (%)	
Acute lymphoblastic leukemia	21 (39.6)	1st remission	5 (23.8)
		2nd remission	9 (42.9)
		3rd remission	7 (33.3)
Acute myeloid leukemia	15 (28.85)	1st remission	1 (6.7)
		≥2nd remission	11 (73.3)
		not in remission	3 (20)
Aplastic anemia	11 (20.75)	Severe	6 (54.5)
		Very severe	5 (45.5)
Myelodysplastic syndrome	9 (9.46)	Juvenile myelomonocytic leukemia	3 (60)
Primary immunodeficiency	1 (1.9)	Primary severe combined immunodeficiency	1 (1.9)

56.6% of patients (n=30) had a concurrent diagnosis of viral hepatitis before HSCT; all were carriers of cytomegalovirus (CMV) infection (Figure 1).

Considering the distribution by age, most patients (46.15%) were elder children, including 10 to 15 years (35.8%, n=19) and above 15 years (11.3%, n=6). Children of 3 to 7 years accounted for 20.8% (n=11), below 3 years – 18.9% (n=10), and 7 to 10 years – 13.2% (n=7). The median age was 4.7 years. The gender ratio was nearly equal: 47.2% (n = 25) of boys vs. 52.8% of girls.

In 64.1% of cases (n=34), the HSCs were sourced from matched siblings (matched sibling donors (MSD) – 10/10 siblings), in 5.7% (n=3) from matched unrelated donors (matched unrelated donors (MUD)), in 28.3% (n=15) from partially matched related donors (haploidentical parents), and in 1.9% (n=1) from a matched family donor 10/10 (MFD) (Figure 2).

60.4% (n=32) of donors were males, and 39.6% (n=21) were females. The mean age of MSD donors was 10 years (n=34), MUD donors were 29 years (n=3), and one MFD donor was 43 years old. At the same time, the median age of donors for haploidentical HSCT was 35 years (Figure 3).

In transplantations from matched donors (MD), 89.5% (n=34) of hematopoietic stem cells (HSCs) originated from bone marrow, whereas 10.5% (n=4) were derived from peripheral blood HSCs.

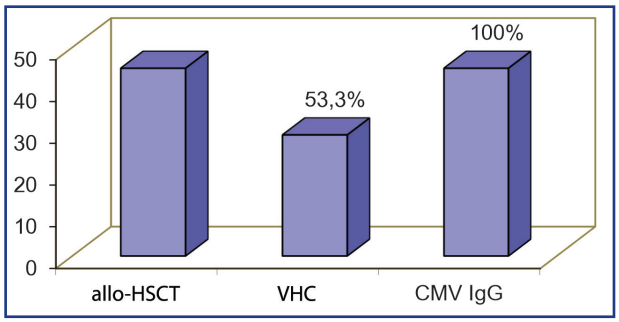

Figure 1 – Concurrent viral infections.

Notes: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; VHC, viral hepatitis C; CMV IgG, cytomegalovirus immunoglobulin.

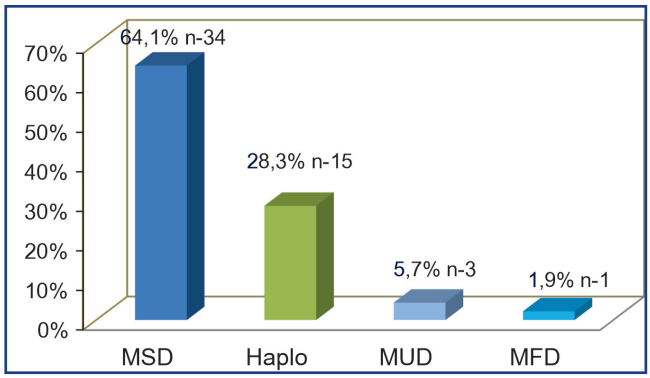

Figure 2 – Structure of HSC donors

Notes to Figures 3-5: HSCs, hematopoietic stem cells; MSD, matched sibling donors; Haplo, partially matched donor (parents); MUD, matched unrelated donors; MFD, matched family donor 10/10.

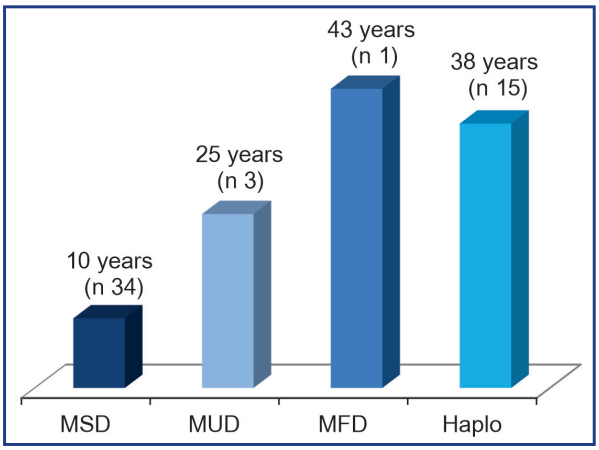

Figure 3 – Median age of HSC donors for allo-HSCT

In haploidentical HSCT, αβ/CD19-depleted peripheral blood-derived HSCs were utilized in 66.7% of cases (n=10), whereas in 33.3% of cases (n=5) HSCs were isolated from bone marrow (Figure 4).

Engraftment was evaluated by neutrophil count (absolute count >500-1000) and platelet count (>20x10^9/l). On average, engraftment of hematopoietic stem cells in peripheral circulation occurred by +15 days and in bone marrow by +30 days following hematopoietic stem cell transplantation. Engraftment in bone marrow hematopoietic stem cell transplantation from matched sibling donors occurred on average by +22 days (range 14-35 days). In bone marrow haploidentical HSCT, engraftment was achieved by day +38, while in haploidentical HSCT with αβ/CD19 depletion, it was attained by day +15 (Figure 5).

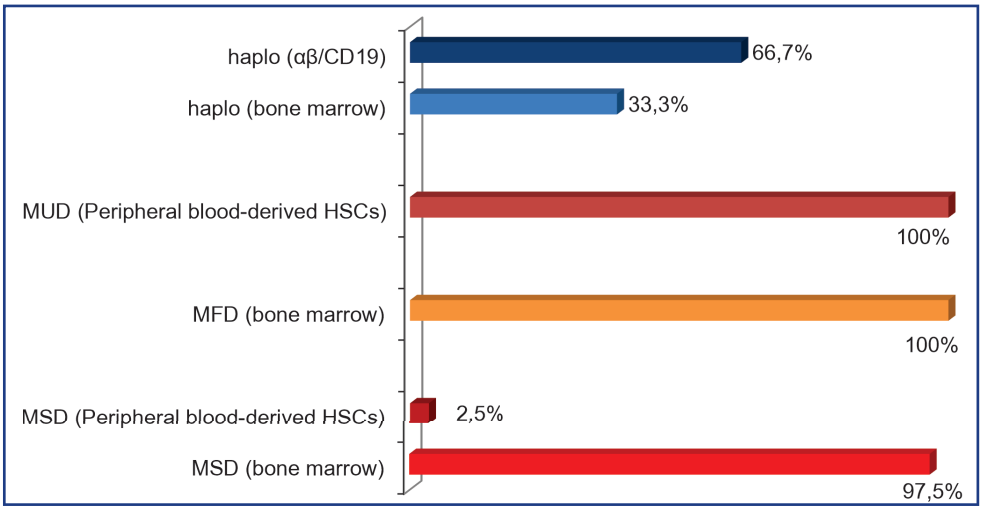

Figure 4 – Characteristics of HSC sources for allo-HSCT

During the engraftment phase, CMV activated in 37.7% (n=20) of patients, Epstein-Barr virus – in 7.5% (n=4), and herpes simplex virus – in 5.7% (n=3). After HSCT, all patients (100%) exhibited a varied reduction in B- and T-cell components of immunity and disruption of cell subpopulation ratios (Figure 6).

The mortality rate from CMV in the early post-transplant interval was 5.7% (n=3).

Acute graft-versus-host disease (GVHD) is critical for survival and treatment efficacy prognosis. In our study, grade I-II GVHD occurred in 9.4% of cases (n=5), and chronic GVHD also manifested in 9.4% of cases (n=5). A case has been reported where acute GVHD coexisted with microangiopathic damage syndrome during GVHD treatment with concurrent CMV activation.

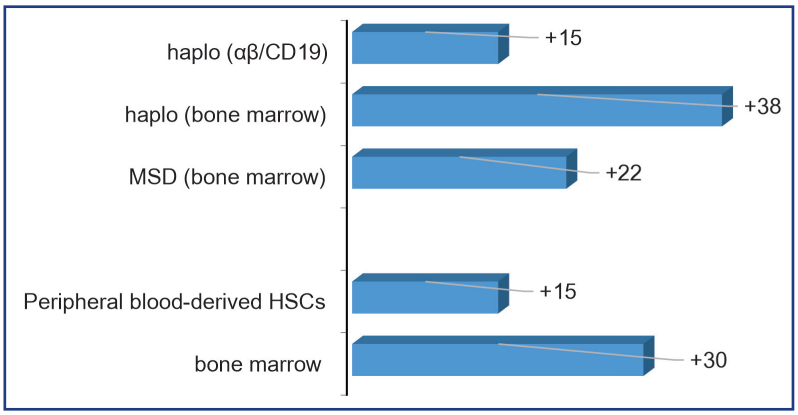

Figure 5 – Engraftment of the graft

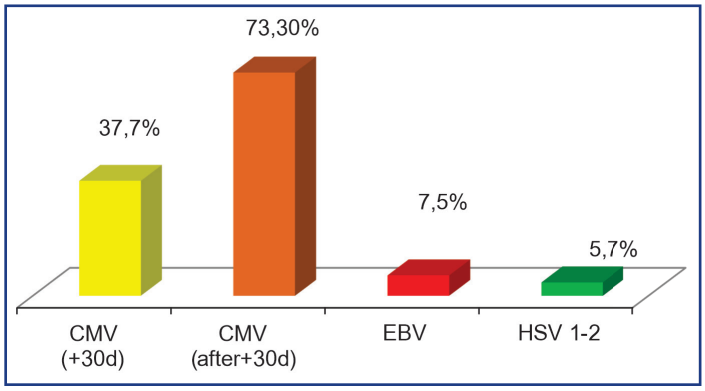

Figure 6 - Activation of viral infection after graft engraftment

Notes: CMV – cytomegalovirus infection; EBV – Epstein-Barr virus; HSV – herpes simplex virus

Recurrences of AL (n=36) post-allo-HSCT were documented in 47.2% of cases (n=17). A patient experiencing a recurrence underwent a second transplantation.

The overall survival percentage of patients following allo-HSCT from a matched donor was 55.2% (n=21), whereas from a related matched donor, it was 57.1% (n=20).

The survival rate of patients with severe and supersevere aplastic anemia was 63.6% (n= 7/11).

The overall survival rate for patients with ALL receiving transplants from matched-related donors was 63.6% (n=7). It was observed during the categorization of patients based on the interval between the onset of the disease and HSCT that the cohort of children who received HSCT at an earlier disease stage (n=6) exhibited a survival rate of 83.3%, whereas those in the third remission undergoing HSCT (n=5) demonstrated a survival rate of merely 40%.

Discussion: HSCT is essential in managing patients with oncohematological diseases since it can markedly increase patient survival rates. HSCT is a necessary stage of therapy for high-risk oncohematological disorders in their early stages, as well as for disease relapses. Still, HSCT efficacy depends on many parameters, including the disease type, conditioning regimens, complications like GVHD, infections, etc. The success of HSCT is contingent upon prior therapy, which must be systematic, comprehensive, adhere to contemporary standard guidelines, and be administered promptly. The authors previously disclosed the initial findings of the allo-HSCT trial involving 42 patients with oncohematological disorders [4]. Prior research revealed higher post-transplantation mortality, which could be due to more inclusive candidate selection criteria for allo-HSCT. This provides foundations for the study of the determinants influencing the success and efficacy of allo-HSCT in pediatric patients.

Furthermore, overall survival rates were not considered. The study's findings indicate that the overall survival rate for patients with ALL receiving transplants from matched related donors was 63.6% with allo-HSCT. In contrast, those undergoing HSCT at the earliest stages of the disease exhibited significantly higher survival rates of 83.3% compared to patients who received transplants during the third remission. To ensure successful graft engraftment, HSCT in pediatric patients with aplastic anemia should be conducted promptly after the disease onset, with minimal hematological burden.

Conclusion: The present study was a retrospective analysis of risk factors influencing the efficacy of allo-HSCT in pediatric patients. In the future, the rise in HSC transplantation necessitates comprehensive studies that consider new factors, an expanded patient pool that has undergone allo HSCT, and the creation of risk assessment

scales for the disease. Generally, it is important to acknowledge that children necessitating HSC transplantation differ markedly from adults in several aspects. It renders the application of calculated disease risk indices from adults to infants unfeasible [5, 6]. A specific approach is required, preferably coordinated among various centers [7]. Future plans include enhancing HSCT technology in pediatric patients through diverse conditioning regimens, incorporating immunotherapy, including bridge therapy, increasing transplantation volume based on indications, and advancing unrelated HSCT and haploidentical transplantation. It is imperative to prioritize the implementation of molecular genetic diagnostics for pediatric oncohematological diseases in our country to stratify risk groups and ascertain minimal residual disease, utilizing next-generation sequencing technologies. The challenges of implementing and augmenting the number of HSCTs in children within the Republic of Kazakhstan are pertinent and require additional efforts to guarantee a tailored treatment approach, thereby enhancing survival rates, prolonging life expectancy, and mitigating the risk of adverse and severe treatment complications in pediatric patients.

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АҢДАТПА

ПЕДИАТРИЯ ЖӘНЕ БАЛАЛАР ХИРУРГИЯСЫ ҒЫЛЫМИ ОРТАЛЫҒЫНЫҢ КЛИНИКАСЫНДА БАЛАЛАРҒА АЛЛОГЕНДІК ГЕМОПОЭТИКАЛЫҚ ДІҢ ЖАСУШАЛАРЫН ТРАНСПЛАНТАЦИЯЛАУ НӘТИЖЕЛЕРІ

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Өзектілігі: *Өмір сүруді жақсарту үшін аллогендік гемопоэтикалық дің жасушаларын трансплантациялау нәтижелерін және жынысы, кондиция режимі, донорлық үйлесімділік, АГЖТ кезіндегі негізгі аурудың статусы сияқты факторлардың АГЖТ кейін пациенттердің өмір сүру көрсеткіштеріне ықтимал әсерін зерттеу. жоғары қауіпті онкогематологиялық аурулары бар науқастардың нәтижелері мен өмір сүру сапасы.*

Қазақстан Республикасында педиатрия және балалар хирургиясы ғылыми орталығының базасында 2012 жылы педиатриялық науқастарда гемопоэтикалық дің жасушаларын трансплантациялау қолданыла бастады. Мақалада онкогематологиялық патологиясы бар балаларда балалар мен балаларды күту ғылыми орталығының жағдайында аллогенді АГЖТ жүргізу тәжірибесі берілген.

Әдістері: *2012 жылдан 2020 жылға дейін Балалар мен балаларға арналған ғылыми орталықта жүргізілген АГЖТ кейін 53 науқастың бақылау деректеріне ретроспективті талдау.*

Зерттеудің мақсаты *– АГЖТ нәтижелерін және жынысы, кондициялық режимі, донорлық үйлесімділігі, АГЖТ кезіндегі негізгі аурудың жағдайы сияқты факторлардың қауіпті топтағы онкогематологиялық аурулары бар науқастардың өмір сүру көрсеткіштеріне ықтимал әсерін зерттеу. Пациенттің өмір сүруі Каплан-Майер бойынша бағаланды, статикалық өңдеу SPSS Statistic бағдарламасы арқылы жүзеге асырылды.*

Нәтижелері: *Біздің зерттеуімізде науқастардың 39,6% -ында жедел лимфобластикалық лейкоз (БАРЛЫҚ n=21), жедел миелобластикалық лейкозбен (ЖМЛ) 28,85% (n=15) пациенттер диагнозы қойылды, апластикалық анемия үшін аллоHSCT 20,75% жағдайда орындалды (n =11), 9,46% (n =5) миелодиспластикалық синдромға (MDS) АГЖТ жасалды, оның ішінде үш пациентте (60%) кәмелет-*

ке толмаған миеломоноцитарлық лейкоз (JMML) болды. Зерттеу нәтижелеріне сәйкес, алло- АГЖТ жүргізген кезде, үйлесімді туыстық донордан ALL бар науқастардың жалпы өмір сүру деңгейі 63,6% құрады, ал аурудың басталуынан бастап ең ерте кезеңде АГЖТ жасағанда, өмір сүру деңгейі айтарлықтай болды. жоғары (83,3%). АГЖТ тиімділігіне трансплантацияға дейінгі емдеу және толық үйлесімді донордың болуы да әсер етті. Апластикалық анемияда терапияның басталу уақыты маңызды фактор болып табылады.

***Қорытынды:** АГЖТ ерте кезеңдерінде және аурулардың қайталануы жағдайында жоғары тәуекел топтарының онкологиялық және гематологиялық ауруларын емдеудің қажетті кезеңі болып табылады. АГЖТ оң нәтиже алдыңғы терапияға байланысты, яғни. емдеу бағдарламалық, толық көлемде, заманауи стандартты хаттамаларға сәйкес және уақытылы жүргізілуі керек. Қазақстан Республикасында балаларда жүргізілетін ЖҚТК енгізу және санын арттыру мәселелері өзекті болып табылады және өмір сүру ұзақтығын, күтілетін өмір сүру ұзақтығын жақсартуға, педиатриялық ауруларда қажетсіз және қауіпті асқынулардың даму қаупін азайтуға жекелендірілген тәсілді қамтамасыз ету үшін одан әрі күш салуды талап етеді.*

***Түйін сөздер:** гемопоэтикалық дің жасушаларын трансплантациялау, балалар, жедел лейкоз, онкогематологиялық аурулар.*

АННОТАЦИЯ

РЕЗУЛЬТАТЫ АЛЛОГЕННОЙ ТРАНСПЛАНТАЦИИ ГЕ-МОПОЭТИЧЕСКИХ СТВОЛОВЫХ КЛЕТОК У ДЕТЕЙ В КЛИНИКЕ НАУЧНОГО ЦЕНТРА ПЕДИАТРИИ И ДЕТСКОЙ ХИРУРГИИ

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***Актуальность:** Трансплантация гемопоэтических стволовых клеток (ТГСК) является методом оказания высокоспециализированной помощи пациентам, с онкологическими и гематологическими заболеваниями, тяжелыми комбинированными первичными иммунодефицитами, а также другими врожденными и наследственными болезнями, протекающими с поражением кроветворной и иммунной систем.*

***Цель исследования** – изучить результаты проведенных аллоТГСК и возможное влияние таких факторов, как пол, режим кондиционирования, совместимость донора, статус основного заболевания на момент проведения ТГСК на показатели выживаемости пациентов с онкогематологическими заболеваниями групп высокого риска.*

***Методы:** Ретроспективный анализ данных наблюдений за 53 пациентами с онкогематологической патологией после ТГСК в условиях Научного Центра педиатрии и детской хирургии г. Алматы с 2021-2020 гг. Выживаемость пациентов оценивали по методу Каплана-Майера, статическая обработку проводили с помощью программы SPSS Statistics.*

***Результаты:** Результаты проведенных аллоТГСК были оценены у 39,6% пациентов с острым лимфобластным лейкозом (n=21), у 28,85% пациентов (n=15) с острым миелобластным лейкозом, при апластической анемии в 20,75% случаев (n=11), в 9,46% (n=5) при миелодиспластическом синдроме, из них трое пациентов (60%) с ювенильным миеломоноцитарным лейкозом.*

Общая выживаемость пациентов с острым лимфобластным лейкозом при проведении аллоТГСК от совместимого родственного донора составила 63,6%, при этом показатели выживаемости при проведении ТГСК в наиболее ранние сроки от начала заболевания были значительно выше (83,3%). Так же на эффективность ТГСК влияли лечение до трансплантации, наличие полностью совместимого родственного донора. При апластической анемии значимым фактором являлось время от начала терапии.

***Заключение:** ТГСК является необходимым этапом терапии при онкогематологических заболеваниях групп высокого риска в ранние сроки и при рецидивах заболеваний. Положительный результат ТГСК зависит от ранее проводившейся терапии, т.е. лечение должно быть программным, осуществляться в полном объёме, в соответствии с современными стандартными протоколами и своевременным. В детской практике необходим специализированный подход, в идеале гармонизированный между различными трансплантационными центрами. Вопросы увеличения количества проводимых ТГСК у детей требуют дальнейшего изучения для улучшения выживаемости, продолжительности жизни, снижения риска развития нежелательных осложнений у пациентов детского возраста.*

***Ключевые слова:** трансплантация гемопоэтических стволовых клеток (ТГСК), дети, острый лейкоз, онкогематологические заболевания.*

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