Contents lists available at ScienceDirect

Acta Haematologica Polonica

journal homepage: www.elsevier.com/locate/achaem

Original research article/Praca oryginalna

Role of HLA match on results of hematopoietic stem cell transplantations from unrelated donors in children with acute leukemia and bone marrow failure syndromes

Znaczenie zgodności HLA na wyniki transplantacji komórek hematopoetycznych od dawców niespokrewnionych u dzieci z ostrymi białaczkami i niewydolnościami szpiku

Jan Styczyński [1,*], Robert Dębski [1], Anna Krenska [1], Krzysztof Czyżewski [1], Natalia Bartoszewicz [1], Ewa Demidowicz [1], Ninela Irga-Jaworska [2], Elżbieta Drożyńska [2], Marcin Płonowski [3], Maryna Krawczuk-Rybak [3], Tomasz Ociepa [4], Tomasz Urasiński [4], Mariusz Wysocki [1]

[1] Katedra i Klinika Pediatrii, Hematologii i Onkologii, Collegium Medicum im. L. Rydygiera w Bydgoszczy, Uniwersytet Mikołaja Kopernika, Szpital Uniwersytecki nr 1 im. Jurasza w Bydgoszczy, Kierownik: prof. dr hab. n. med. Mariusz Wysocki, Poland
[2] Katedra i Klinika Pediatrii, Hematologii i Onkologii, Uniwersytet Medyczny, Kierownik: prof. dr hab. n. med. Elżbieta Adamkiewicz-Drożyńska, Gdańsk, Poland
[3] Klinika Onkologii Dziecięcej, Uniwersytet Medyczny, Kierownik: prof. dr hab. n. med. Maryna Krawczuk-Rybak, Białystok, Poland
[4] Katedra i Klinika Pediatrii, Hematologii i Onkologii, Pomorski Uniwersytet Medyczny, Kierownik: prof. dr hab. n. med. Tomasz Urasiński, Szczecin, Poland

A R T I C L E I N F O

A B S T R A C T

Background: In case of the lack of matched family donors (MFD), hematopoietic stem cell transplantation (HSCT) from unrelated donor (UD) is an established procedure for many acquired and congenital disorders of the hematopoietic system, including malignances and bone marrow failure (BMF) syndromes. Objective: The analysis of the results of HSCT in patients with acute leukemia or BMF syndromes from UDs with respect to human leukocyte antigen (HLA) match. Patients and methods: A total number of 97 of HSCT from UDs performed in single center between 2007 and 2015 in children and adolescents with acute lymphoblastic (ALL) or myeloblastic leukemia (AML) and BMF syndromes were included into this analysis. HLA match between donor and recipient was

* Corresponding author at: Katedra Pediatrii, Hematologii i Onkologii, Collegium Medicum im. L. Rydygiera w Bydgoszczy, Uniwersytet Mikołaja Kopernika, ul. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, Poland.
    E-mail address: jstyczynski@cm.umk.pl (J. Styczyński).

- Children
- Adolescents and young adults

---

analyzed at the allele level and classified as 10/10, 9/10 or 8/10. Data were compared to results of 56 MFD-HSCTs. Probability of overall survival (pOS) was given for 3-year and 1-year (as required by JACIE standards) time periods. **Results:** The mean survival for all patients estimated by Kaplan–Meier method was 4.8 years (95%CI = 4.1–5.5 years). The 3-year pOS after all UD-HSCT was 0.60 ± 0.05, and with respect to 10/10, 9/10 and 8/10 HLA match: 0.61 ± 0.06; 0.59 ± 0.09 and 0.60 ± 0.22, respectively (ns). In patients with AML, 3-year pOS reached 52%, 60% and 60%, respectively. In patients with ALL, 3-year pOS was 73% and 62% (ns) for 10/10 and 9/10 HLA match, respectively, while for BMF syndromes 86% and 57% (ns), respectively. **Conclusion:** Current data suggest that results of mismatched and matched UD-HSCT in children with acute leukemia might be comparable.

Introduction

By the end of 2012, more than 1 million transplants has been done at 1516 transplant centers in total 75 countries performing HSCTs [1]. The number of allogeneic transplantations performed in Poland in 2015 was 605 including 411 from unrelated donors (UD), 169 from (MFD), and 25 haploidentical transplants [2]. In our Department we had started transplant program with MFD allogeneic HSCT in 2003, autologous HSCT in 2004 and UD-HSCT in 2007 [3].

Allogeneic hematopoietic stem cell transplantation (HSCT) remains a curative option for children with high risk and advanced acute lymphoblastic (ALL) and myeloblastic leukemia (AML) and bone marrow failure syndromes (BMF). For patients who lack a human leukocyte antigen (HLA) matched family donor (MFD), a transplant from an alternative donor remains the best therapeutic options. Over last decade HSCT from UD has become an established method of treatment for refractory blood diseases, with the aim of achieving long-term survival.

HLA match between donor and recipient is a major factor contributing to success of HSCT and the use of an HLA 10 of 10 allele-matched UD is obviously recommend worldwide. High-resolution HLA-matching significantly impacts outcome and also may predict for non-relapse mortality and overall survival (OS).

This is however not possible in all UD-HSCT. If such a donor is not available, any single-allele or multiple-allele (HLA-C, -DRB1, -DQB1) mismatched donor out of 10 HLAs is acceptable as an UD for patients with severe aplastic anemia [4]. In patients with ALL, AML, and myelodysplastic syndromes (MDS) matching for HLA-A, -B, -C, and -DRB1 alleles (8/8 match) was associated with better survival at 1 year compared with 7/8 HLA-matched pairs [5, 6]. HLA-C antigen mismatch was associated with worse outcome in UD peripheral blood stem cell transplantation, however HLA mismatch was not associated with relapse or chronic graft-versus-host disease (GVHD) [5].

The objective of this study was the analysis of the results of stem cell transplantation in patients with acute leukemia or BMF syndromes from UD with respect to HLA match in single pediatric center.

Methods

Patients

Between 2003 and 2015 a total number of 318 transplants were performed in our Department, including 186 allo-HSCT and 132 auto-HSCT. Program of HSCTs from UD has begun in 2007. All transplants performed for patients with ALL, AML, MDS or BMF/SAA from UD between 2007 and 2015 in our Department were included in this analysis. Transplants performed with cord blood were excluded from this analysis.

Demographics

The number of UD-HSCT performed for ALL, AML/MDS or BMF/SAA was 97, including 43 for ALL (25 in complete remission CR1, 18 CR $\geq$ 2), 40 for AML/MDS (AML: 13 CR1, 18 CR $\geq$ 2, 3 secondary AML; MDS: 3 JMML, 2 RCMD, 1 RAEB) and 14 for BMF/SAA (11 acquired SAA, 1 PRCA, 1 Fanconi anemia, 1 Schwachman-Diamond syndrome). A second or subsequent transplant was performed in 12 cases (3/18 AML-CR $\geq$ 2, 8/18 ALL-CR $\geq$ 2, 1/2 MDS-RCMD). The recipients of transplants were males in 67 transplants and females in 30 cases. The median age of transplant recipients was 10.5 years (range: 0.8–22 years). The source of hematopoietic stem cells was peripheral blood in 75 patients (77%), and bone marrow in 22 patients (23%). The median follow-up was 1.4 years (range: 0.1–7.6 years).

Transplant procedures

Patients underwent HSCT according to procedures described previously [3] and standard infectious prophylaxis were used [7–9]. Cyclosporine $\pm$ methotrexate were used for GVHD prophylaxis. In all patients *in vivo* T-cell depletion was performed before UD-HSCT with rabbit ATG (Genzyme) in total dose 8 mg/kg for $\geq$9/10 HLA match and in dose 12 mg/kg for 8/10 HLA match. The follow-up was censored at 29 February 2016.

HLA typing

High-resolution DNA-based 4-digit typing was performed for 5 pairs of loci: HLA-A, -B, -Cw, -DRB1 and -DQB1. HLA match

between donor and recipient was analyzed at the allele level and classified as 10/10, 9/10 or 8/10.

End points

OS was set as the primary end point. OS was defined as time from transplantation to death or last follow-up. Neutrophil recovery was defined as an absolute neutrophil count (ANC) of at least 0,5 G/L for three consecutive days. Platelet recovery was defined as a count of at least 20 G/L without platelet transfusion support for 7 days. Acute GVHD (aGVHD) was defined in accordance with standard criteria. Chronic GVHD (cGVHD) was evaluated in patients surviving for more than 100 days after allo-HCT and was classified as limited or extensive type.

Statistical analysis

Probability of overall survival (pOS) and probability of event-free survival (pEFS) was calculated using the Kaplan–Meier method and compared with the log-rank tests. Mean survival was also determined by Kaplan–Meier method, with 95% confidence interval (CI). Rate of survivors in analyzed time periods was compared with chi-square test. All p-values are 2-tailed and considered statistically significant if the values were less than 0,05. All statistical analyses were performed using the SPSS23 software (SPSS Inc, Chicago, IL, USA).

Results

Engraftment

The cumulative probabilities of neutrophil and platelet recovery were 91.6% and 78.5%, respectively. The median time to neutrophil recovery (ANC > 500) was 19 days (range, 10–29), while the median time to platelet engraftment (platelet count >20 G/L) was 15 days (range, 10–65).

Graft-versus-host disease

The cumulative probabilities of aGVHD and extensive cGVHD were 17.7% and 5.4%, respectively: 19/97 (19.6%) patients developed aGVHD grade II or higher, including 11 (11.3%) with grade III or IV, while 4/72 (5.5%) evaluable patients developed extensive cGVHD.

Mortality

A total of 63/97 (64.9%) transplants were not associated with mortality at the time of this analysis. A thirty-four patients (35.1%) had died due to transplant-related complications ($n = 26$) or disease relapse/progression ($n = 8$). The cumulative probability of transplant related mortality (TRM) was 24.7% (24/97) at one year: 18 patients (18.5%) died within the first 100 days post-HCT, including 1 patient (1%) who died before day 30.

OS and event-free survival

The mean survival for all patients estimated by Kaplan–Meier method was 4.8 year (95%CI = 4.1–5.5 years). pOS after all transplants was $0,60 \pm 0,05$. Taking all patients together, pOS after allo-HSCT with 10/10, 9/10 and 8/10 HLA match was $0,61 \pm 0,06$; $0,59 \pm 0,09$ and $0,60 \pm 0,21$, respectively ($p = 0,912$) (Table I). In patients with AML, 3-year OS reached 52%, 60% and 60%, respectively. In patients with ALL 3-year OS was 73% and 62% for 10/10 and 9/10 HLA match, respectively, and for BMF syndromes 86% and 57%, respectively. No differences were observed in OS between patients transplanted before the end of 2012 and afterwards (Fig. 1). Respective values for pEFS are presented in Table II.

Transplant-related mortality

Out of total number of 97 transplants, in 34 (35%) cases the treatment was unsuccessful. Treatment-related deaths occurred in 22 (22.7%) cases, including 2/5 (40%) patients with 8/10 HLA-matched HSCT, 8/30 (26.7%) patients with 9/10 HLA-matched HSCT, and 12/62 (19.3%) patients with 10/10 HLA-matched HSCT. The number of progression-related deaths in patients with acute leukemia was 12/83 (14.5%), including 4/43 with ALL (2/13 in 9/10 HLA-matched HSCT; 2/30 in 10/10 HLA-matched HSCT) and 8/40 with AML (0/5 in 8/10 HLA-matched HSCT; 2/10 in 9/10 HLA-matched HSCT; 6/25 in 10/10 HLA-matched HSCT). The causes of treatment-related deaths 2 patients with 8/10 HLA-matched HSCT included: PTLD ($n = 1$) and sepsis with multi-organ failure (MOF) after primary graft failure ($n = 1$). The causes of treatment-related deaths 8 patients with 9/10 HLA-matched HSCT included: septic shock with MOF ($n = 3$), pneumonia ($n = 3$) with CMV or fungal infection, post-transplant lymphoproliferative disorder (PTLD) ($n = 1$), and brain-stem

Table I – Results of HSCT with respect to HLA match				
Diagnosis	Probability of 3-year overall survival			p
	HLA 8/10	HLA 9/10	HLA 10/10	
Acute lymphoblastic leukemia	–	$0,62 \pm 0,13$ (8/13)	$0,73 \pm 0,08$ (22/30)	0,562
Acute myeloid leukemia	$0,60 \pm 0,22$ (3/5)	$0,60 \pm 0,15$ (6/10)	$0,52 \pm 0,18$ (14/25)	0,975
Bone marrow failure syndromes	–	$0,57 \pm 0,19$ (4/7)	$0,86 \pm 0,13$ (6/7)	0,258
Total	$0,60 \pm 0,22$ (3/5)	$0,59 \pm 0,09$ (18/30)	$0,61 \pm 0,06$ (42/62)	0,912

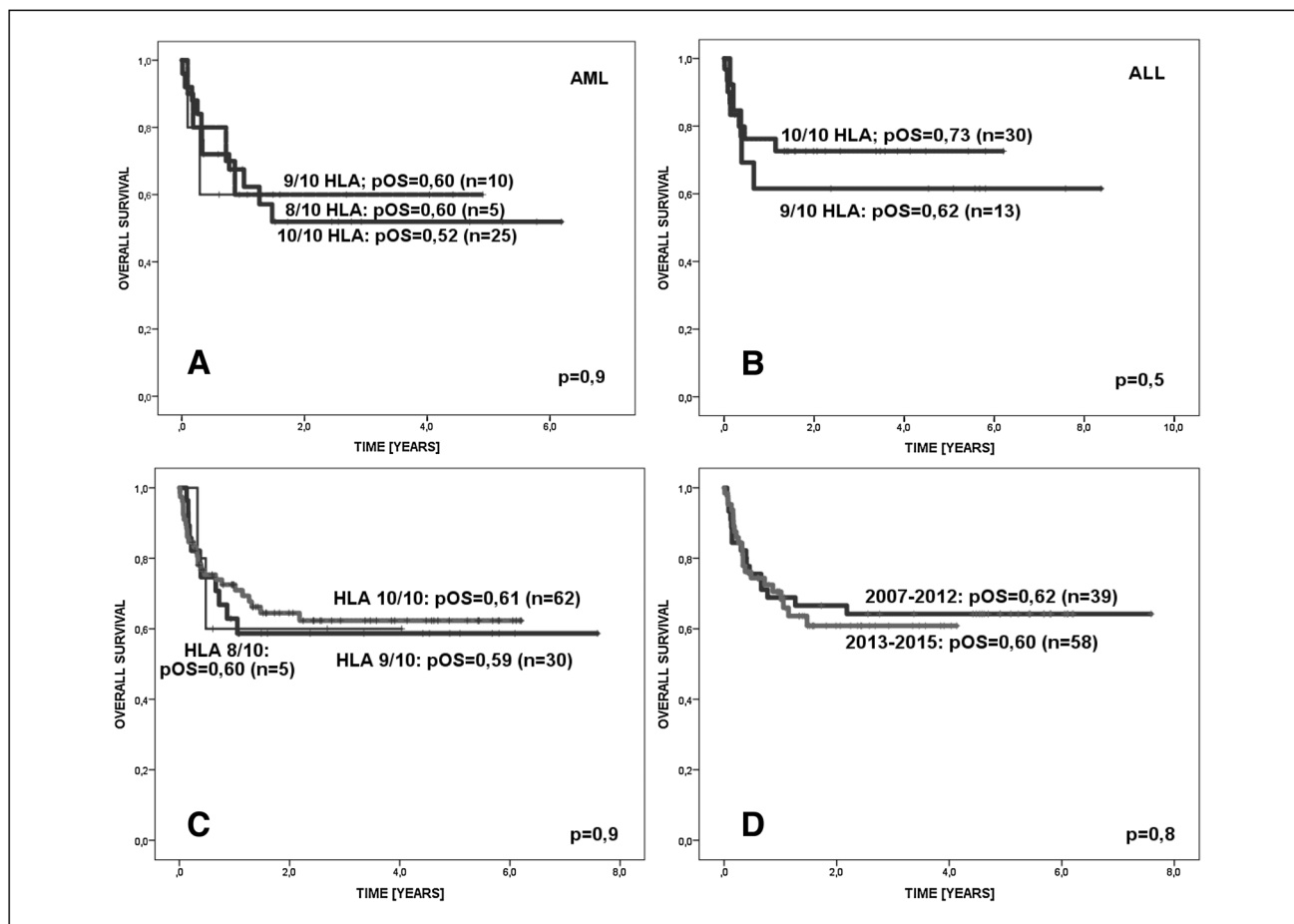Number of surviving and all patients with respective diagnoses are provided in parentheses.

Fig. 1 – Results of HSCT with respect to HLA match: (A) in AML, (B) in ALL, (C) in all patients together, (D) in all patients together with respect to period of transplantation

ischemic stroke ($n = 1$). The causes of treatment-related deaths 12 patients with 10/10 HLA-matched HSCT included: septic shock with MOF ($n = 3$), pneumonia ($n = 4$) with CMV or fungal infection, PTLD with MOF ($n = 2$), GVHD with MOF ($n = 2$), sinusoid obstructive syndrome (SOS) with MOF ($n = 1$).

One-year OS and event-free survival: comparison to other types of transplant. According to recent version of JACIE standards requirements, one-year survival rates were calculated and compared to other types of transplants performed in our center. One-year survival for all 318 patients transplanted in our center between 2003 and 2015 was $0{,}768 \pm 0{,}024$; for allo-HSCT $0{,}710 \pm 0{,}034$, and for auto-HSCT $0{,}850 \pm 0{,}032$. Estimated 5-year pOS after all allo-HSCT performed between 2003 and 2015 in our Department was $0{,}62 \pm 0{,}04$. With respect to HLA donor match in HSCT from UD, 1-year survival was $0{,}709 \pm 0{,}052$; $0{,}629 \pm 0{,}094$ and $0{,}600 \pm 0{,}219$ for 10/10, 9/10, and 8/10 HLA match, respectively. Results of probability of 1-year OS and probability of 1-year event-free survival for patients with ALL, AML/MDS and BMF/SAA transplanted either from MFD or from UD are shown in Tables III and IV.

Table II – Results of EFS with respect to HLA match				
Diagnosis	Probability of 3-year event-free survival			p
	HLA 8/10	HLA 9/10	HLA 10/10	
Acute lymphoblastic leukemia	–	$0{,}62 \pm 0{,}13$ ($n = 13$)	$0{,}73 \pm 0{,}08$ ($n = 30$)	0,562
Acute myeloid leukemia	$0{,}60 \pm 0{,}22$ ($n = 5$)	$0{,}40 \pm 0{,}16$ ($n = 10$)	$0{,}33 \pm 0{,}11$ ($n = 25$)	0,826
Bone marrow failure syndromes	–	$0{,}57 \pm 0{,}19$ ($n = 7$)	$0{,}86 \pm 0{,}13$ ($n = 7$)	0,258
Total	$0{,}60 \pm 0{,}22$ ($n = 5$)	$0{,}52 \pm 0{,}09$ ($n = 30$)	$0{,}57 \pm 0{,}06$ ($n = 62$)	0,716

Number of all patients with respective diagnoses are provided in parentheses.

Table III – One-year survival			
Diagnosis	MFD-HSCT	UD-HSCT	Total
Acute lymphoblastic leukemia	0,68 ± 0,10 (n = 23)	0,72 ± 0,07 (n = 43)	0,71 ± 0,06 (n = 66)
Acute myeloid leukemia	0,84 ± 0,08 (n = 19)	0,61 ± 0,08 (n = 40)	0,68 ± 0,06 (n = 59)
Bone marrow failure syndromes	0,92 ± 0,07 (n = 14)	0,66 ± 0,13 (n = 14)	0,78 ± 0,08 (n = 28)
Total	0,79 ± 0,05 (n = 56)	0,67 ± 0,05 (n = 97)	0,71 ± 0,04 (n = 153)
Number of patients with respective diagnoses is provided in parentheses.			

Table IV – One-year event-free survival			
Diagnosis	MFD-HSCT	UD-HSCT	Total
Acute lymphoblastic leukemia	0,54 ± 0,11 (n = 23)	0,70 ± 0,07 (n = 43)	0,64 ± 0,08 (n = 66)
Acute myeloid leukemia	0,79 ± 0,09 (n = 19)	0,56 ± 0,08 (n = 40)	0,63 ± 0,07 (n = 59)
Bone marrow failure syndromes	0,92 ± 0,07 (n = 14)	0,66 ± 0,13 (n = 14)	0,78 ± 0,08 (n = 28)
Total	0,75 ± 0,06 (n = 56)	0,65 ± 0,06 (n = 97)	0,66 ± 0,06 (n = 153)
Number of patients with respective diagnoses is provided in parentheses.			

Discussion

In this study we analyzed results of transplants from UD performed in our center in children and adolescents with acute leukemia or BMF syndromes with respect to HLA match. In this small series of children we have shown that OS might not significantly differ with the respect to the level of HLA match, however current literature data demonstrate that still the level of HLA mismatches may, together with other factors, demonstrate impact on results of UD-HSCT. The UD-HSCT results could also be compared with those performed from MFD-HSCT. Probability of 3-year overall survival (pOS) after all transplants from UD shown in this study was 0,61 ± 0,06, while 3-year pOS after all MSD-HSCT performed between 2003 and 2015 in our Department was 0,73 ± 0,04 (p = 0,044, data not shown). Application of transplants from UD in our center in 2007 has enlarged therapeutic possibilities for our patients. Since pediatric patients are expected to live for a long time after HSCT and the recent data have not shown any positive correlation between cGVHD and relapse in a landmark analysis of long-term survivors with the exception of chronic myeloid leukemia (CML) [10], the low rate of cGVHD in our series should also be noted.

Over this period of time we faced also an international trend in increase of the number of HSCTs from UD exceeding number of transplants from sibling donors. With the increase in the number of donors in Polish registries over 1 million in April 2016, nowadays most of our UD are from Poland. However, even with high resolution typing of HLA and better donor match, the risk of GVHD is higher in case of transplants performed from UD than sibling donors; this might lead to an increase in the risk of other complications such as life-threatening infections. Thus, it is difficult to indicate if transplants from UD improve the results of OS. Still, the number of patients with transplant-related mortality is too high, and there is an international need in improving supportive therapy for transplanted patients.

Report from the leading Swedish center indicated three-year OS in 2003–2013 for children with malignant disorders to be 68% and for nonmalignant disorders 87% [11], while in French center overall 5-year OS was 64% for children transplanted between 2000 and 2010 [12]. The improvement in outcome was also observed in our Department over the analyzed period of 12 years, as the 5-year OS of patients undergoing allo-HSCT before the year 2007 was 43%, what shows growing experience and abilities of our transplant team, both doctors and nurses [13]. Probability of OS of HSCT patients in our transplant center showed results comparable with EBMT centers. This is valuable achievement since nowadays more and more patients with more complex diagnoses are being qualified for transplantation, such as multiple-relapsed patients or those with advanced disease or co-existing comorbidities. It is an international trend that more and more patients are qualified for second and subsequent transplant.

In summary, the presented results of HSCT obtained in our center are comparable with those from major international centers. One HLA mismatch between donor and recipient is not an obstacle to perform transplant for children with acute leukemia in terms of OS after allogeneic transplant. Current improvement in HSCT outcome is dependent not only on very good donor match but also multidirectional and interdisciplinary supportive care.

Authors' contributions/Wkład autorów

JS had primary responsibility for study design and manuscript preparation. All authors participated in the project and contributed to data collection and interpretation.

Conflict of interest/Konflikt interesu

None declared.

REFERENCES/PIŚMIENNICTWO

[1] Gratwohl A, Pasquini MC, Aljurf M, Atsuta Y, Baldomero H, Foeken L, et al. One million haemopoietic stem-cell transplants: a retrospective observational study. Lancet Haematol 2015;2:e91–e100.

[2] Łęczycka A, Dudkiewicz M. Rejestr przeszczepień komórek krwiotwórczych szpiku i krwi obwodowej oraz krwi pępowinowej. Biuletyn informacyjny Poltransplant. Warszawa 2016;24:74–83.

[3] Styczyński J, Dębski R, Krenska A, Górnicka H, Hulek E, Wojtylak P, et al. Transplantacje komórek hematopoetycznych w świetle 5-letnich doświadczeń. Med Biol Sci 2008;22:157–163.

[4] Yagasaki H, Kojima S, Yabe H, Kato K, Kigasawa H, Sakamaki H, et al. Acceptable HLA-mismatching in unrelated donor bone marrow transplantation for patients with acquired severe aplastic anemia. Blood 2011;118:3186–3190.

[5] Woolfrey A, Klein JP, Haagenson M, Spellman S, Petersdorf E, Oudshoorn M, et al. HLA-C antigen mismatch is associated with worse outcome in unrelated donor peripheral blood stem cell transplantation. Biol Blood Marrow Transplant 2011;17:885–892.

[6] Lodewyck T, Oudshoorn M, van der Holt B, Petersen E, Spierings E, von dem Borne PA, et al. Predictive impact of allele-matching and EBMT risk score for outcome after T-cell depleted unrelated donor transplantation in poor-risk acute leukemia and myelodysplasia. Leukemia 2011;25:1548–1554.

[7] Styczyński J, Reusser P, Einsele H, de la Camara R, Cordonnier C, Ward KN, et al. Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia. Bone Marrow Transplant 2009;43:757–770.

[8] Styczyński J, Gil L. Prevention of infectious complications in pediatric HSCT. Bone Marrow Transplant 2008;42(Suppl. 2): S77–S81.

[9] Ljungman P, de la Camara R, Cordonnier C, Einsele H, Engelhard D, Reusser P, et al. Management of CMV, HHV-6, HHV-7 and Kaposi-Sarcoma Herpesvirus (HHV-8) infections in patients with hematological malignancies and after SCT. Bone Marrow Transplant 2008;42:227–240.

[10] Boyiadzis M, Arora M, Klein JP, Hassebroek A, Hemmer M, Urbano-Ispizua A, et al. Impact of chronic graft-versus-host disease on late relapse and survival on 7,489 patients after myeloablative allogeneic hematopoietic cell transplantation for leukemia. Clin Cancer Res 2015;21:2020–2028.

[11] Svenberg P, Remberger M, Uzunel M, Mattsson J, Gustafsson B, Fjaertoft G, et al. Improved overall survival for pediatric patients undergoing allogeneic hematopoietic stem cell transplantation – a comparison of the last two decades. Pediatr Transplant 2016;20:667–674.

[12] Brissot E, Rialland F, Cahu X, Strullu M, Corradini N, Thomas C, et al. Improvement of overall survival after allogeneic hematopoietic stem cell transplantation for children and adolescents: a three-decade experience of a single institution. Bone Marrow Transplant 2016;51:267–272.

[13] Styczyński J, Dębski R, Krenska A, Czyżewski K, Kołtan S, Irga-Jaworska N, et al. Improvement of cure after hematopoietic stem cell transplantations in children. Med Biol Sci 2016;30:51–56.