Medical and Biological Sciences, 2012, 26/4, 41-46

ORIGINAL ARTICLE / PRACA ORYGINALNA

Jan Styczyński[1,2], Robert Dębski[1,2], Anna Krenska[1,2], Krzysztof Czyżewski[1,2], Ewa Dembna[2], Ninela Irga[3], Magdalena Szalewska[3], Elżbieta Adamkiewicz-Drożyńska[3], Marcin Płonowski[4], Elżbieta Leszczyńska[4], Maryna Krawczuk-Rybak[4], Agnieszka Żyromska[5], Barbara Drzewiecka[5], Karolina Majewska[5], Wiesława Windorbska[5], Mariusz Wysocki[2]

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATIONS IN ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN AND ADOLESCENTS

TRANSPLANTACJE ALLOGENICZNYCH KOMÓREK HEMATOPOETYCZNYCH W OSTREJ BIAŁACZCE LIMFOBLASTYCZNEJ U DZIECI I MŁODZIEŻY

[1]Katedra Pediatrii, Hematologii i Onkologii, Collegium Medicum im. L. Rydygiera w Bydgoszczy, Uniwersytet Mikołaja Kopernika
Kierownik: prof. dr hab. n. med. Mariusz Wysocki
[2]Szpital Uniwersytecki nr 1 im. Jurasza, Bydgoszcz
Dyrektor: mgr Jarosław Kozera
[3]Katedra i Klinika Pediatrii, Hematologii, Onkologii i Endokrynologii, Uniwersytet Medyczny, Gdańsk
Kierownik: prof. dr hab. n. med. Elżbieta Adamkiewicz-Drożyńska
[4]Klinika Onkologii i Hematologii Dziecięcej, Uniwersytet Medyczny, Białystok
Kierownik: prof. dr hab. n. med. Maryna Krawczuk-Rybak
[5]Centrum Onkologii, Bydgoszcz
Dyrektor: dr n. med. Zbigniew Pawłowicz

S u m m a r y

B a c k g r o u n d . ALL is the most common indication for allogeneic hematopoietic stem cell transplantation (allo-HSCT) in children.

O b j e c t i v e . The analysis of results of therapy in children and adolescents treated for ALL with allo-HSCT.

P a t i e n t s a n d m e t h o d s . A total number of 41 patients undergoing allo-HSCT due to ALL between 2003 and 2012. In 17 patients HSCT was performed from related donor and in 24 from unrelated donor. A source of hematopoietic stem cells was peripheral blood in 21 patients, bone marrow in 18 patients and cord blood in 2 patients.

R e s u l t s . At present, 27 (65.8%) patients stay alive. Among 14 deaths, 8 were regarded as transplant-related mortality, and 6 as a relapse of disease. Transplant-related mortality was 8/41 (19.5%), including 7 (17%) in early post-transplant period (before day +100). Probability of survival for all patients was: pDFS=0.652±0.091 (mean disease-free-survival was 3.8 years, 95%CI=2.7-4.8), pOS=0.630±0.080 (mean survival 3.9 years, 95%CI=3.0-4.8). The only factor predicting overall survival was time of pre-transplant relapse: for very early relapses pOS=0.333±0.157, for early relapses pOS=0.666±0.272 and for late relapses pOS=0.833±0.152 (p=0.010).

C o n c l u s i o n s . Allo-HSCT from well-matched unrelated donors or genoidentical sibling donors is an effective treatment with acceptable toxicity in pediatric ALL. Precise HLA typing and matching resulted in a low incidence of acute and extensive chronic GVHD which is an important achievement for the quality of life in children and adolescents. The results from this study demonstrate the feasibility of a harmonized HSCT approach in pediatric ALL.

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Streszczenie

Wstęp. Ostra białaczka limfoblastyczna (ALL) jest najczęstszym wskazaniem do przeszczepiania allogenicznych hematopoetycznych komórek macierzystych (allo-HSCT) u dzieci.

Celem pracy była analiza wyników leczenia ALL u dzieci poddawanych allo-HSCT w ośrodku bydgoskim.

Pacjenci i metodyka. Badaniami objęto 41 pacjentów leczonych w latach 2003-2012. W 17 przypadkach wykonano transplantację od dawcy rodzinnego, a w 24 od dawcy niespokrewnionego. Źródłem komórek hematopoetycznych była krew obwodowa u 21 pacjentów, szpik kostny u 18 pacjentów oraz krew pępowinowa u 2 pacjentów.

Wyniki. W momencie zakończenia analizy żyło 27 (65,8%) pacjentów. Spośród 14 zgonów, 8 było zależnych od procedur transplantacyjnych, a 6 od wznowy choroby podstawowej. Śmiertelność zależna od powikłań transplantacyjnych wyniosła 8/41 (19,5%), w tym 7 (17%) we wczesnym okresie poprzeszczepowym (do dnia +100). Prawdopodobieństwo przeżycia dla całej badanej grupy wyniosło: pDFS=0,652±0,091 (średnie przeżycie bez wznowy 3,8 lat, 95%CI=2,7-4,8 lat), pOS=0,630±0,080 (średnie przeżycie 3,9 lat, 95%CI=3,0-4,8 lat). Jedynym czynnikiem prognostycznym terapii był czas wystąpienia wznowy kwalifikującej do transplantacji: dla wznów bardzo wczesnych pOS=0,333±0,157, dla wznów wczesnych pOS=0,666±0,272 i dla późnych pOS=0,833±0,152 (p=0,010).

Wnioski. Allo-HSCT od zgodnych dawców rodzinnych lub niespokrewnionych jest efektywną terapią o akceptowalnej toksyczności w ALL. Precyzyjny dobór dawcy skutkuje niskim odsetkiem ostrej i przewlekłej GVHD, co może wpływać na jakość życia. Wyniki przeprowadzonej analizy pokazują kierunki terapii z zastosowaniem HSCT w ALL u dzieci i młodzieży.

Key words: hematopoietic stem cell transplantation, children, adolescents, acute lymphoblastic leukemia
Słowa kluczowe: przeszczepianie komórek hematopoetycznych, dzieci, młodzież, ostra białaczka limfoblastyczna

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer. Despite significant improvement in therapy for what once was a uniformly fatal disease, still 20-25% of children with ALL relapse. It makes relapsed ALL the fifth most common pediatric cancer (after initial ALL, brain tumor, Non-Hodgkin Lymphoma and Hodgkin Disease) [1]. ALL is also the most common indication for allogeneic hematopoietic stem cell transplantation (allo-HSCT) in children, as about 30% of all allo-HSCT in children is performed due to this disease [2]. Indications for HSCT in ALL are poor response to induction treatment, cytogenetic aberrations t(9;22) or t(4;11), early bone marrow relapse, or any subsequent ALL relapse.

The objective of the study was the analysis of results of therapy in children and adolescents treated for ALL with allo-HSCT in Department of Pediatric Hematology and Oncology in Bydgoszcz.

METHODS

Patients

Forty-one patients including 25 (61%) males and 16 (39%) females, undergoing allogeneic hematopoietic stem cell transplantations (HSCT) for ALL between 2003- and 2012 were pooled into the analysis.

The median age at time of allo-HCT was 8.3 (range 0.8-20) years. Fourteen (34%) transplants were performed at first remission (CR1), 27 (66%) in second or subsequent (≥CR2) remission. One patient had congenital leukemia. Two patients were diagnosed for chromosomal instability syndromes: Nijmegen syndrome and Ataxia-Teleangiectasia syndrome. Patients with bilineage leukemia were excluded from this analysis. Three patients underwent second transplant. Among patients qualified for transplant with ≥CR2, 9 had very early relapse, 7 early relapse and 9 late relapse.

Conditioning

Preparative regimen before HSCT was done according to standard EBMT (European Blood and Marrow Transplantation group) protocols. The backbone conditioning regimen was based on total body irradiation (TBI/etoposide), used for 18 patients (1200 cGy for total body irradiation). TBI was performed in the Oncology Center in Bydgoszcz. For other preparative regimens, 19 patients received myeloablative busulfan-based conditioning (total oral dose 16 mg/kg, or intravenous busilvex at weight-adapted schedule), and 4 patients received fludarabine-based reduced toxicity conditioning due to comorbidities.

Stem cell source

The stem cells for the 16 patients were from HLA-matched family sibling donor (MFD), for 1 patient from haploidentical parent, and for 24 patients from HLA-matched unrelated donor (MUD). Unrelated donors matched in 9/10 HLA (n=3) loci were regarded as matched donors [3]. The source of stem cells was peripheral blood (PB) in 21 cases, bone marrow (BM) in 18 cases and cord blood (CB) in 2 cases.

Cell dose

For PB-HSCT, the median dose of mononuclear cells (MNC) transplanted was 12.49 (range: 4.31-25.1) x 10^8/kg and median dose of CD34 cells was 8.30 (range: 3.90-23.36) x 10^6/kg. For BM-HSCT, the median dose of MNC and CD34 cells was 5.85 (range: 1.67-14.27) x 10^8/kg and 3.07 (range: 0.35-8.95) x 10^6/kg, respectively. For CBT, the median dose of MNC and CD34 cells was 5.9 (range: 4.1-7.7) x 10^7/kg and 1.2 (range: 0.8-1.6) x 10^5/kg, respectively.

Transplant procedures

Patients underwent HSCT according to the procedures described previously [4-7]. Standard infectious prophylaxis was used [8]. GVHD prophylaxis was CsA-based in all patients (with short-term methotrexate in 31 cases after transplants PB or BM). All patients receiving transplant from unrelated donor received antithymocyte globulin. Unrelated CBT was followed by CsA±methylprednisolone prophylaxis. Keratinocyte growth factor (palifermin) [9] was administered prophylactically in 31 (75.6%) patients.

Very early relapse was defined as occurring during 18 months from the initial diagnosis; early BM relapse as occurring in less than 6 months after the cessation of therapy of leukemia, and a late BM relapse, when occurred later. BM relapse included isolated BM or combined (BM and central nervous system or testis) relapses. For patients transplanted in third remission (CR3), assignment to early or late groups was based on their first relapse. All patients gave their consent before transplant.

End points

Overall survival (OS) was set as the primary end point. OS was defined as time from transplantation to death or last follow-up. Disease free survival (DFS) was defined as time from the transplantation to disease relapse or last follow-up. Non-relapse mortality (NRM) was defined as a death not related to disease. Transplant-related mortality (TRM) was defined as death related to transplant complications. Neutrophil recovery was defined as an absolute neutrophil count of at least 0.5 G/L for two consecutive days. Platelet recovery was defined as a count of at least 20 G/L without 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 into limited or extensive type.

Statistical analysis

Patients and disease's characteristics were summarized using descriptive statistics. Mean survival was determined by Kaplan-Meier method, with 95% confidence interval (CI). The primary endpoints were DFS and OS. Other endpoints included TRM, risk of relapse, acute GVHD (aGVHD) and chronic GVHD (cGVHD). Cumulative incidence was used to estimate relapse, TRM, aGVHD and cGVHD. Kaplan-Meier was used to estimate OS and DFS. Statistical comparison of OS and DFS between groups was completed by the log-rank test. The proportional hazards model of Cox was used to assess the independent factors on relapse, TRM, aGVHD and cGVHD. Factors included in multivariate analysis were: CR status, recipient CMV status, transplant cell source, OS, DFS, TRM, aGVHD and cGVHD. The backwards-stepwise method was used to determine the final model and all statistical analyses were implemented using the SPSS20 software (SPSS Inc, Chicago, IL, USA). In all statistical tests, a P-value of 0.05 was considered significant.

RESULTS

Engraftment

Neutrophil engraftment was achieved in 39 of 41 transplants. The median time to neutrophil recovery was 17 days (range, 11-29). In a total of 7 patients, a platelet count >20 G/L was not reached. In the patients that achieved platelet counts of >20 G/L, the median time to platelet engraftment was 19 days (range, 9-65). The cumulative probabilities of neutrophil and platelet recovery were 95% and 83%, respectively.

GVHD

Eight (19.5%) patients developed aGVHD grade II or higher, including 3 (7.3%) with grade III or IV,

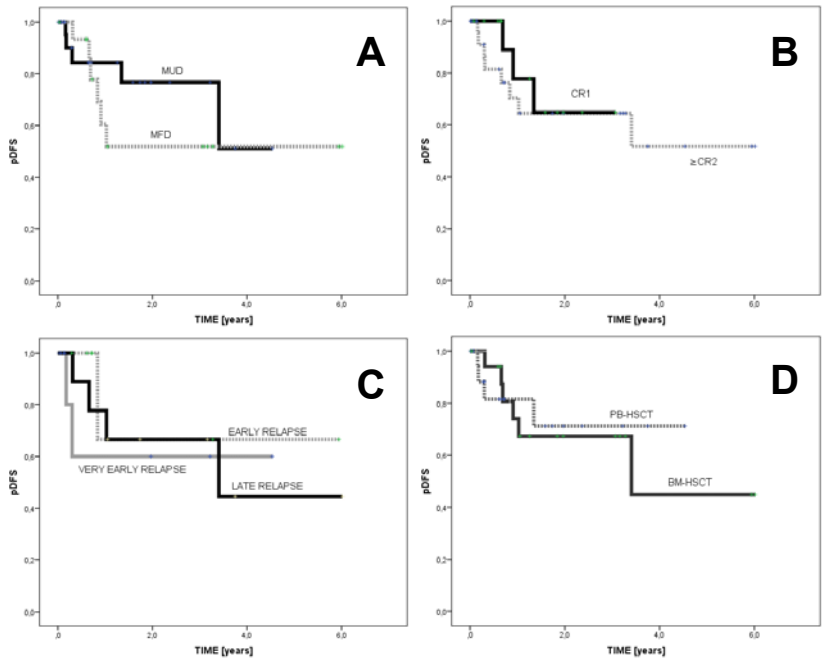

Fig. 1. *Probability of disease-free survival (pDFS) after HSCT in ALL, with respect to: (A) donor type, (B) first remission and relapsed disease, (C) timing of the pre-transplant disease, (D) stem cell source*

Ryc. 1. *Prawdopodobieństwo przeżycia wolnego od choroby po HSCT w ALL, w odniesieniu do: (A) rodzaju dawcy, (B) fazy choroby, (C) rodzaju wznowy przed przeszczepem, (D) źródła komórek*

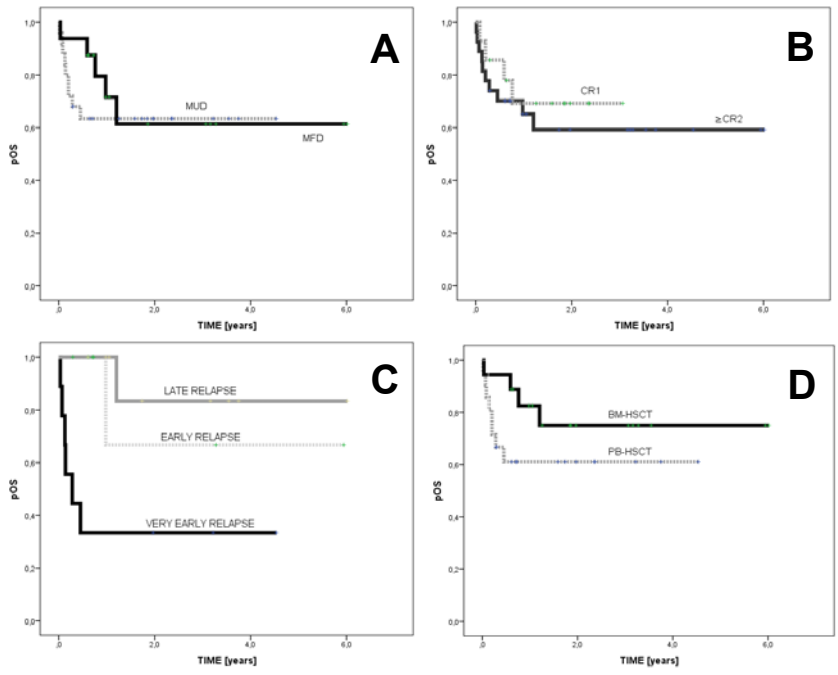

Fig. 2. *Probability of overall survival (pOS) after HSCT in ALL, with respect to: (A) donor type, (B) first remission and relapsed disease, (C) timing of the pre-transplant disease, (D) stem cell source*

Ryc. 2. *Prawdopodobieństwo przeżycia po HSCT w ALL, w odniesieniu do: (A) rodzaju dawcy, (B) fazy choroby, (C) rodzaju wznowy przed przeszczepem, (D) źródła komórek*

extensive cGVHD. The cumulative probabilities of aGVHD≥2 and extensive cGVHD were 19.5% and 13%, respectively.

Disease-free survival

Relapse after HSCT has occurred in 11 (26.8%) patients. The 3-year pDFS was 0.652±0.091. The mean DFS was 3.8 years (95%CI=2.7-4.8). Patients undergoing HSCT from their sibling donors (MFD) had pDFS=0.519±0.144, while those after unrelated donor transplants had pDFS=0.767±0.105 (p=0.426) (Fig.1A). Patients at CR1 had pDFS=0.684±0.165, while those at CR≥2 had pDFS=0.645±0.110 (p=0.602) (Fig. 1B). For patients transplanted due to relapse, type of relapse had no impact on pDFS. For very early relapses pDFS=0.600±0.218 (n=2/9 relapses), for early relapses pDFS=0.667±0.272 (1/7 relapses) and for late relapses pDFS=0.667±0.157 (3/9 relapses plus one relapse at 3.4 years after HSCT) (p=0.722) (Fig.1C). Patients who received PB-HSCT had pDFS=0.713±0.128, while those after BM-HSCT had pDFS=0.672±0.121 (p=0.310) (Fig.1D).

Overall survival

The median follow-up was 12 months (range: 0-72 months). The 3-year pOS=0.630±0.080. Fourteen (65.8%) patients died after HSCT, however excluding patients undergoing second HSCT who were analyzed separately, no death occurred later than 15 months after HSCT. The mean survival was 3.9 years (95%CI=3.0-4.8 years). Patients

undergoing HSCT from their sibling donors (MFD, matched family donors) had pOS=0.614±0.141, while those after unrelated donor transplants had pOS=0.635±0.097 (p=0.579) (Fig.2A). Patients at CR1 had pOS=0.693±0.129, while those at CR≥2 had pOS=0.592±0.103 (p=0.519) (Fig.2B). For patients transplanted due to relapse, time of relapse had an impact on pOS. For very early relapses pOS=0.333±0.157 (n=6/9 deaths), for early relapses pOS=0.666±0.272 (1/7 deaths) and for late relapses pOS=0.833±0.152 (1/9 deaths) (p=0.010) (Fig.2C). Patients who received PB-HSCT had pOS=0.611±0.108, while those after BM-HSCT had pOS=0.750±0,110 (p=0.050) (Fig.2D).

Mortality

A total of 27/41 (65.8%) patients were alive at the time of this analysis, while 14 had died due to transplant-related complications (n=8) or disease relapse/progression (n=6). The cumulative probability of transplant related mortality (TRM) was 19.5% at one year. The relapse incidence was 14.6%. Seven patients (17%) died within the first 100 days post-HCT, including 4 patients (9.7%) who died before day 30.

Patients transplanted without complete remission

Five patients were qualified for HSCT with partial remission (blast percentage: 7-15%). All of them died, including two who died due to transplant-related complications 5-13 days after HSCT, two died in relapse 2-11 months after HSCT and one died due to sepsis complicated with possible pulmonary embolism.

Second transplants

Three patients underwent second HSCT due to post-transplant relapse. Two patients who relapsed 5-17 months after HSCT, had second transplant from the same donor 12-21 months after first HSCT. Both stayed in CR2 for 7-10 months after HSCT. One patient transplanted at CR3, relapsed 8 months after HSCT, underwent second HSCT 4 months later, then relapsed 15 months later and died.

Uni- and multivariate analyses

No factor was significant in univariate analysis for DFS. The only factor significant for OS was time of relapse (for CR2 patients) with relapse risk 10 (95%CI=1.2-84) for very early relapse and 1.6 (95%CI=0.1-26) for late relapse as baseline (p=0.040).

DISCUSSION

In spite of good prognosis in pediatric ALL, still about 20-25% of patients relapse. For majority of them, HSCT is the only curative option, and thus ALL is the most frequent pediatric indication for HSCT. The first transplant performed in Pediatric BMT Unit in Bydgoszcz on 8 October 2003 was done in ALL patient carrying BCR-ABL rearrangement. In January 2012, the number of patients transplanted with stem cells in the Unit reached 200. Patients with ALL were subjects of HSCTs in overall 44 (22%) cases, including 42% of all allo-HSCTs (data unpublished).

Recently published results of multicenter European study for children with ALL treated by allo-HSCT [3] showed equivalent to our center's transplant outcome, with probability of event-free 70% survival after MFD-HSCT and 68% after MUD-HSCT. The incidence of GVHD was similar. Acute GVHD>2 grade occurred in 20% of all patients, and the 2-year cumulative incidence of extensive chronic GVHD was 15% after MFD and 12% after MUD-HSCT. The cumulative incidence of treatment related mortality after 1-year was 5% for MFD and 8% for MUD-HSCT and was lower than in our center. The 2-year cumulative incidence of relapse was higher, reaching 18% after MFD-HSCT and 20% after MUD-HSCT. Comparably to our results, patients with very high relapse risk had 2-year event-free survival in only 28%. In multivariate analysis for event free survival, no statistically significant difference was seen for patients older than 12 years, T-ALL, BCR-ABL or MLL-rearrangement [3]. This report indicates that transplant outcome in our center is similar to that of multicenter European; however TRM in our center is higher, while relapse incidence is lower. Further improvement in HSCT outcome will be dependent on both very good donor match and multidirectional and interdisciplinary supportive care [10-12] as well as new therapeutic, diagnostic and supportive care modalities [13-14].

We demonstrated that allogeneic HSCT from well-matched unrelated donors or genoidentical sibling donors is an effective treatment with acceptable toxicity. Precise HLA typing and matching, and use of antithymocyte globulin resulted in a low incidence of extensive chronic GVHD, which is an important achievement for the quality of life of children and adolescents. The results from this study demonstrate the feasibility of a harmonized HSCT approach in pediatric hematology and oncology centers.

ACKNOWLEDGEMENTS

We thank the nursing staff of the Pediatric BMT Team for their outstanding, support and care showed to our patients, and physicians from the Department of Pediatric, Hematology and Oncology at the Jurasz University Hospital of Bydgoszcz for their continuous support for transplant center.

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Address for correspondence:
Prof. dr hab. n. med. Jan Styczyński
Katedra Pediatrii, Hematologii i Onkologii
Collegium Medicum im. L. Rydygiera w Bydgoszczy
Uniwersytet Mikołaja Kopernika
ul. Curie-Skłodowskiej 9
85-094 Bydgoszcz
e-mail: jstyczynski@cm.umk.pl
tel: (52) 585 4860
fax: (52) 585 4867

Received: 10.07.2012
Accepted for publication: 21.08.2012