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HIGH-DOSE THERAPY AND AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION RESCUE IN CHILDREN WITH NEUROBLASTOMA AND EWING SARCOMA

TERAPIA WYSOKODAWKOWA Z PRZESZCZEPIENIEM AUTOLOGICZNYCH KOMÓREK KRWIOTWÓRCZYCH U DZIECI Z NERWIAKIEM ZARODKOWYM I MIĘSAKIEM EWINGA

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Summary

Background. High-dose therapy (HDT) with autologous stem cell rescue has been recently applied in very-poor-risk pediatric solid tumors. Promising data have become available with the use of high-dose busulfan in neuroblastoma (NBL) and Ewing sarcoma (ES), and with high-dose treosulfan in ES. HDT approach resulted in an encouraging outcome without toxic mortality for high-risk patients.

Objective. The objective of this study is to present transplant outcomes, that is disease-free-survival and overall survival in children with high-risk NBL and ES undergoing auto-HSCT.

Patients and methods. A total number of 47 NBL and 20 ES auto-HSCT performed between 2004 and 2016 in a single transplant center were included in this analysis.

Results. Probability of 3-years pOS was 0.79±0.06 and 0.46±0.14 for NBL and ES patients, respectively. Relapse incidence at 3 years after HSCT was 0.37±0.08 and 0.26±0.11 for NBL and ES patients, respectively. The number of relapses at 3 years after HSCT was 15/47 in NBL and 6/20 in ES. Busulfan-based vs treosulfan-based conditioning in ES patients resulted in lower relapse and death rates. NBL and ES patients transplanted in complete remission (CR1) had lower relapse rates and lower death rates than patients at CR>1.

Conclusion. Obtained results of auto-HSCT confirm the therapeutic benefit for children with NBL and ES. Recent reports on current practice of HSCT in Europe indicate HDT with auto-HSCT as a standard of care in pediatric patients with high risk or relapsed NBL and ES.

Streszczenie

Wstęp. Terapia wysokodawkowa (HDT) i transplantacja autologicznych komórek krwiotwórczych (auto-HSCT) została wprowadzona w leczeniu dzieci ze źle rokujacymi guzami litymi. Wstępne dane wskazują na wartość HDT opartej na busulfanie w neuroblastoma (NBL) i mięsaku Ewinga (ES) oraz zastosowaniu treosulfanu w ES. HDT z auto-HSCT stwarza możliwości poprawy wyników terapii przeciwnowotworowej, bez dodatkowej śmiertelności u pacjentów wysokiego ryzyka niepowodzenia terapeutycznego.

Celem pracy była analiza wyników terapii u dzieci z NBL i ES poddawanym HDT i auto-HSCT.

Pacjenci i metodyka. Analizie poddano wyniki przeszczepień wykonanych u 47 dzieci z NBL i 20 z ES leczonych w latach 2004-2016 w pojedynczym ośrodku.

Wyniki. Prawdopodobieństwo całkowitego 3-letniego przeżycia wyniosło odpowiednio 0,79±0,06 i 0,46±0,14 u dzieci z NBL i ES. Kumulacyjna częstość wznów w okresie 3-letnim wyniosła odpowiednio 0,37±0,08 i 0,26±0,11 u dzieci z NBL i ES. Liczba wznów w tym okresie wyniosła 15/47 w NBL i 6/20 w ES (ns).

U pacjentów z ES kondycjonowanie oparte na busulfanie przyniosło niższy odsetek wznów i zgonów niż kondycjonowanie oparte na treosulfanie. Pacjenci z NBL i ES poddawani transplantacji w CR1 mieli niższy odsetek wznów i zgonów niż pacjenci z CR>1.

W n i o s k i . Wyniki HDT z auto-HSCT potwierdzają korzyść terapeutyczną u dzieci z NBL i ES. Aktualne analizy europejskie wskazują, że takie postępowanie zostało uznane za standard opieki u dzieci z tymi chorobami.

Key words: hematopoietic stem cell transplantation, high-dose therapy, children, neurolastoma, Ewing sarcoma
Słowa kluczowe: przeszczepianie komórek krwiotwórczych, terapia wysokodawkowa, dzieci, nerwiak płodowy, mięsak Ewinga

INTRODUCTION

High-dose therapy (HDT) with autologous stem cell rescue has been recently applied in very-poor-risk pediatric solid tumors. Promising data have become available with the use of high-dose busulfan in neuroblastoma (NBL) and Ewing sarcoma (ES), with high-dose treosulfan in ES, whereas high-dose (HD) thiotepa was less commonly used. HDT approach resulted in an encouraging outcome without toxic mortality for high-risk patients [1].

NBL is a childhood cancer with remarkably divergent tumour behaviour and the presence of metastatic disease is a powerful predictor of adverse outcome [2]. Despite the development of new treatment options, the prognosis of high-risk NBL patients is still poor; more than half of patients experience disease recurrence. High-dose chemotherapy (i.e. myeloablative therapy) and hematopoietic autologous stem cell transplantation (auto-HSCT) as a rescue is expected to improve the survival [3].

ES is the second most common type of primary bone malignancy in children and young adults. Survival rates for localized ES have improved to upwards of 70% with aggressive chemotherapy and local control. On the other hand, there has been little improvement in survival rates for patients with metastatic or recurrent ES. The treatment of ES family of tumors is multimodal, both in children and adults. Axial location and metastases are classic prognostic factors. However, the worse prognosis in older patients is more controversial. Induction chemotherapy with the VIDE regimen was feasible in most patients, with a low risk for early progression. Hematological toxicity was substantial but manageable. It should be noted that adult patients had a worse prognosis, and also survival after progression is dismal [4].

The objective of this study is to present transplant outcomes, that is disease-free-survival and overall survival in children with high-risk NBL and ES undergoing auto-HSCT.

METHODS

All auto-HSCT performed between due to NBL or ES between 2004-2016 in Department of Pediatric Hematology and Oncology in Bydgoszcz were included in this analysis. The results of therapy with stem cell transplantation were analyzed in three time periods: 2004-2007, 2008-2011 and 2012-2016; all consecutive transplants were included into each time period. Patients underwent HSCT according to procedures described previously [5-8]. The follow-up was censored at 28 November 2016.

Statistical analysis. Overall survival (OS) was set as the primary end point, and defined as time from transplantation to patient's death or last follow-up. Probability of overall survival (pOS), relapse incidence, and probability of disease-free survival were 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). Rates of survivors in analyzed time periods were 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 SPSS22 software (SPSS Inc, Chicago, IL, USA).

RESULTS

Demographics. A total number of auto-HSCT performed between 2004 and2016 was 47 for NBL and 20 for ES. All but three patients underwent one transplant; 2 patient had two transplants (1 NBL, 1 ES), and 1 had three transplants (1 NBL). The recipients of transplants were males in 28 NBL and 8 ES transplants and females in 19 NBL and 12 ES cases. The median age of transplant recipients was 3,7 years (range 0.7-16 years) for NBL, and 15 years (range 3.2-18 years) for ES. The source of hematopoietic stem cells was PB in 44 NBL and 19 ES patients, BM in 3 NBL and 1 ES patients. The median follow-up was 3.1 years (range: 0.1-12.5 years) for NBL and 1.5 years (range: 0.1-12.1 years) for ES. With

respect to phase of the disease, 31 NBL patients were in CR1 and 16 in CR>1, while 11 ES patients were in CR1 and 9 in CR>1.

Overall survival. The mean survival estimated by Kaplan-Meier method was 8.8 years (95%CI=7.1-10.6 years) for NBL patients, and 6.3 years (95%CI=3.5-9.1 years) for ES patients. With respect to time period, pOS after auto-HSCT was the highest in the last period of time, both for NBL and ES (Table 1). Probability of 3-years pOS for NBL patients was 0.79±0.06, while 0.46±0.14 for ES patients (p=ns) (Table 2). There was three late (>3 years after HSCT) deaths in NBL patients, which occurred between 3.5-4.4 years after HSCT, while there were no late deaths in ES. Relapse incidence at 3 years after HSCT was 0.37±0.08 for NBL patients, and 0.26±0.11 for ES patients. The number of relapses at 3 years after HSCT was 15/47 in NBL and 6/20 in ES (p=ns). Additionally, there was one late relapse in NBL patient (at 4 years) and there were no late relapses in ES. Busulfan-based vs. treosulfan-based conditioning in ES patients resulted in lower relapse rate (0/5 vs 2/9, p=ns) and lower death rate (0/5 vs 4/9, p=ns). ES patients transplanted in complete remission (CR1) had lower relapse rate (2/11 vs 2/8, i.e. 82% vs 75%, p=ns) and lower death rate (2/11 vs 6/9, i.e. 82% vs 33%, p=0.027; OR=9, 95%CI=0.8-90). NBL patients transplanted in CR1 had lower relapse rate (9/31 vs 7/16, i.e. 71% vs 56%, p=ns) and lower death rate (6/31 vs 6/16, i.e. 81% vs 63%, p=ns) than patients at CR>1.

Table 1. *Results of auto-HSCT with respect to diagnosis and period of therapy*

Tabela 1. *Wyniki auto-HSCT w zależności od choroby podstawowej i okresu terapii*

Diagnosis *Rozpoznanie*	Probability of overall survival *Prawdopodobieństwo przeżycia*			p
	2004-2007	2008-2011	2012-2016	
Neuroblastoma	0,45±0,13 (n=18)	0,75±0,15 (n=8)	0,95±0,11 (n=21)	0,143
Ewing Sarcoma	0,60±0,22 (n=5)	0,23±0,19 (n=8)	0,85±0,13 (n=7)	0,626

n - liczba pacjentów

Mortality. There were 20 deaths in total, including 12 in NBL and 8 in ES patients, due to transplant-related complications (3/20 including 1/12 in NBL and 2/8 in ES, p=ns) or disease relapse/progression (17/20 including 11/12 in NBL and 6/8 in ES, p-ns). Deaths due to transplant-related complications occurred at 2, 6, and 8 months after HSCT.

Table 2. *Transplant outcomes in NBL and ES after auto-HSCT*

Tabela 2. *Wyniki przeszczepień w NBL i ES po auto-HSCT*

Diagnosis Rozpoznanie	Probability of overall survival Prawdopodobieństwo przeżycia		Relapse incidence Prawdopodobieństwo wznowy choroby		Probability of disease-free survival Prawdopodobieństwo przeżycia wolnego od wznowy	
	1-year	3-years	1-year	3-years	1-year	3-years
Ewing Sarcoma	0.84±0.09	0.46±0.14	0.26±0.11	0.26±0.11	0.74±0.11	0.74±0.11
Neuroblastoma	0.81±0.06	0.79±0.06	0.26±0.07	0.37±0.08	0.74±0.07	0.63±0.08

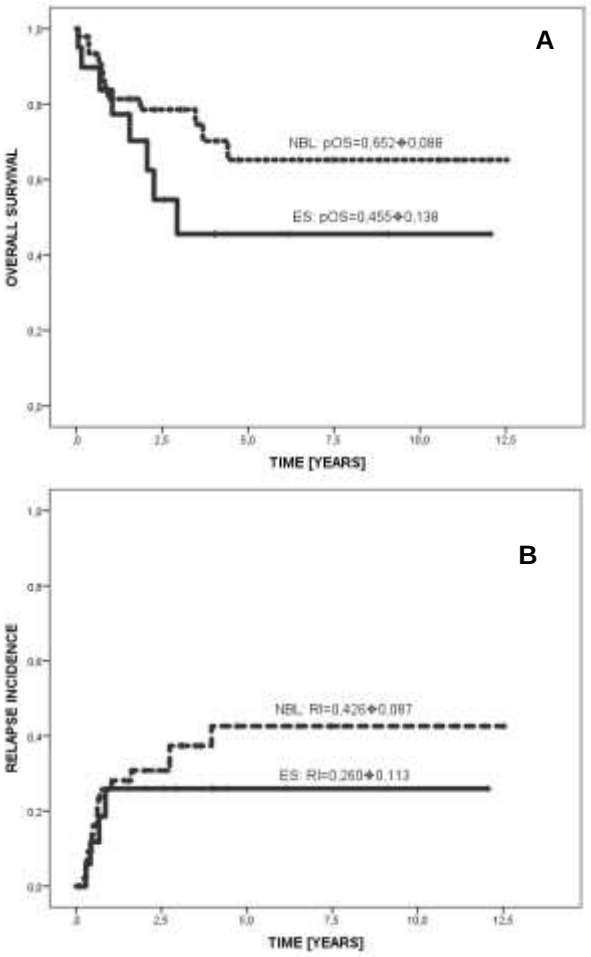

Fig. 1. *Kaplan-Meier plots: (A) probability of overall survival after auto-HSCT; (B) relapse incidence*

Ryc. 1. *Krzywe Kaplana-Meiera i prawdopodobieństwo: (A) przeżycia całkowitego po auto-HSCT; (B) wznowy*

DISCUSSION

Although the role of auto-HCT in fourth stage of NBL and ES is well established there is still concern about efficacy and clinical benefit for children with these diseases. Our analysis indicates that auto-HSCT can cure high rate of NBL and ES patients, with low relapse rates and improved survival in patients without a history of prior auto-HSCT [9]. Nevertheless, disease

recurrence remains the most common cause of treatment failure. More data is available for children with NBL undergoing auto-HSCT, while reports on auto-HSCT in ES patients are relatively scanty. Still, allogeneic HSCT after a prior auto-HCT appears to offer minimal benefit to patients with NBL [10].

Estimated 5-year survival rates for patients with non-high-risk and high-risk neuroblastoma are nowadays 90% and <50%, respectively [11]. Based on the currently available evidence, myeloablative therapy seems to work in terms of disease-free survival in NBL [3]. For patients with high-risk NBL treated with chemoradiotherapy, surgery, and auto-HSCT, the addition of anti-disialoganglioside (GD2) immunotherapy plus cytokines is expected to improve survival. Also, upcoming trials will study the incorporation of targeted radionuclide therapy prior to myeloablative chemotherapy into high-risk treatment [11].

In patients with ES, an intensive approach with auto-HSCT is feasible and long-term survival is achievable in >50% of patients [9,12]. The Italian Sarcoma Group and the Scandinavian Sarcoma Group designed a joint study to improve the prognosis for patients with Ewing's family tumors and synchronous metastatic disease limited to the lungs, or the pleura, or a single bone. 5-year event-free survival probability was 0.43 and the 5-year overall survival probability was 0.52 [12].

In the retrospective analysis of 102 patients divided according to the following risk factors: metastatic disease at presentation, feasibility of surgery and histological response after induction, 41 patients were classified as standard risk (SR) patients, while the remaining 61 children, with at least one risk factor, were classified as HR patients. HR group patients were non-randomized and qualified according to the decision of the local clinician to give a conventional consolidation (CC) or to perform high-dose chemotherapy and radiotherapy in selected patients. Twenty-six children were given CC while 35 patients were treated with HDT. The HDT consisted of oral BU 4 mg/kg p.o. in divided doses daily for 4 days (total dose 16 mg/kg) followed by melphalan 140 mg/m^2 i.v. on day -2. Probability of relapse-free survival (RFS) in median observation time was significantly worse in HR patients who were given CC therapy as compared with children with HR features receiving high-dose chemotherapy (0.27 vs 0.66; p=0.008), while pOS was 0.31 vs 0.71 (p=0.007). Patients from the SR group had a probability of RFS of 0.72 and pOS of 0.75 (p=ns). This study confirmed that the consolidation of the first-line treatment with busulfan and melphalan improves the outcome in ES patients with HR features [9]. On the other hand, also in our study busulfan-based conditioning resulted in better survival and lower relapse rate when compared to patients receiving treosulfan-based conditioning. This finding might suggest that for patients with high-risk ES, the use of busulfan during HDT is a better therapeutic option.

In summary, the presented results of auto-HSCT obtained in our center confirm the therapeutic benefit for children with NBL and ES. According to the published recent reports on current practice of HSCT in Europe, HDT with auto-HSCT is a standard of care in pediatric patients with high risk or relapsed NBL and ES [13,14].

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REFERENCES

1. Jahnukainen K, Kallio P, Koivusalo A, Saarinen-Pihkala UM: High-dose thiotepa as consolidation therapy with autologous hematopoietic stem cell transplantation for high-risk Ewing family tumors: Single-institution experience. J Pediatr Hematol Oncol 2015;37:536-542.
2. Morgenstern DA, London WB, Stephens D, Volchenboum SL, Simon T, Nakagawara A, Shimada H, Schleiermacher G, Matthay KK, Cohn SL, Pearson AD, Irwin MS: Prognostic significance of pattern and burden of metastatic disease in patients with stage 4 neuroblastoma: A study from the International Neuroblastoma Risk Group database. Eur J Cancer 2016;65:1-10.
3. Yalcin B, Kremer LC, van Dalen EC: High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma. Cochrane Database Syst Rev 2015:CD006301.
4. Diaz-Beveridge R, Lorente D, Torres B, Canete A, Rodrigo E, Bruixola G, Berlanga P, Reche E, Montalar J, Verdeguer A, Aparicio J: Multimodality treatment of pediatric and adult patients with ewing sarcoma: A single-institution experience. J Pediatr Hematol Oncol 2015;37:e278-284.

5. Styczyński J, Dębski R, Krenska A, Górnicka H, Hulek E, Wojtylak P, Windorbska W, Drzewiecka B, Ostrowski K, Tujakowski J, Marciniak L, Kusza K, Goc M, Prokurat A, Chrupek M, Urasiński T, Peregud-Pogorzelski J, Ociepa T, Krawczuk-Rybak M, Leszczyńska E, Balcerska A, Niedźwiecki M, M. W: Transplantacje komórek hematopoetycznych w świetle 5-letnich doświadczeń Med Biol Sci 2008;22:157-163.
6. Styczynski J, Reusser P, Einsele H, de la Camara R, Cordonnier C, Ward KN, Ljungman P, Engelhard D: 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.
7. Styczynski J, Gil L: Prevention of infectious complications in pediatric HSCT. Bone Marrow Transplant 2008;42 Suppl 2:S77-81.
8. Ljungman P, de la Camara R, Cordonnier C, Einsele H, Engelhard D, Reusser P, Styczynski J, Ward K: Management of CMV, HHV-6, HHV-7 and Kposi-Srcoma Hrpesvirus (HHV-8) infections in patients with hematological malignancies and after SCT. Bone Marrow Transplant 2008;42:227-240.
9. Drabko K, Raciborska A, Bilska K, Styczynski J, Ussowicz M, Choma M, Wojcik B, Zaucha-Prazmo A, Gorczynska E, Skoczen S, Wozniak W, Chybicka A, Wysocki M, Gozdzik J, Kowalczyk J: Consolidation of first-line therapy with busulphan and melphalan, and autologous stem cell rescue in children with Ewing's sarcoma. Bone Marrow Transplant 2012;47:1530-1534.
10. Hale GA, Arora M, Ahn KW, He W, Camitta B, Bishop MR, Bitan M, Cairo MS, Chan K, Childs RW, Copelan E, Davies SM, Perez MA, Doyle JJ, Gale RP, Vicent MG, Horn BN, Hussein AA, Jodele S, Kamani NR, Kasow KA, Kletzel M, Lazarus HM, Lewis VA, Myers KC, Olsson R, Pulsipher M, Qayed M, Sanders JE, Shaw PJ, Soni S, Stiff PJ, Stadtmauer EA, Ueno NT, Wall DA, Grupp SA: Allogeneic hematopoietic cell transplantation for neuroblastoma: The CIBMTR experience. Bone Marrow Transplant 2013;48:1056-1064.
11. Park JR, Bagatell R, London WB, Maris JM, Cohn SL, Mattay KK, Hogarty M: Children's Oncology Group's 2013 blueprint for research: Neuroblastoma. Pediatr Blood Cancer 2013;60:985-993.
12. Luksch R, Tienghi A, Hall KS, Fagioli F, Picci P, Barbieri E, Gandola L, Eriksson M, Ruggieri P, Daolio P, Lindholm P, Prete A, Bisogno G, Tamburini A, Grignani G, Abate ME, Podda M, Smeland S, Ferrari S: Primary metastatic Ewing's family tumors: Results of the Italian Sarcoma Group and Scandinavian Sarcoma Group ISG/SSG iv study including myeloablative chemotherapy and total-lung irradiation. Ann Oncol 2012;23:2970-2976.
13. Passweg JR, Baldomero H, Peters C, Gaspar HB, Cesaro S, Dreger P, Duarte RF, Falkenburg JH, Farge-Bancel D, Gennery A, Halter J, Kroger N, Lanza F, Marsh J, Mohty M, Sureda A, Velardi A, Madrigal A: Hematopoietic SCT in Europe: Data and trends in 2012 with special consideration of pediatric transplantation. Bone Marrow Transplant 2014;49:744-750.
14. Sureda A, Bader P, Cesaro S, Dreger P, Duarte RF, Dufour C, Falkenburg JH, Farge-Bancel D, Gennery A, Kroger N, Lanza F, Marsh JC, Nagler A, Peters C, Velardi A, Mohty M, Madrigal A: Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: Current practice in Europe, 2015. Bone Marrow Transplant 2015;50:1037-1056.

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