

Progress and trends in pediatric hematopoietic cell transplantation in Central-East European countries

Article history:

Received: 25.05.2020

Accepted: 17.06.2020

Krzysztof Czyżewski^{1*},
Petr Sedláček²,
Jaroslav Štěrba³,
Ernest Bilic^{4,5},
Jelena Roganović⁶,
Gergely Krivan⁷,
Jelena Rascon⁸,
Anca Colita⁹,
Janez Jazbec¹⁰,
Peter Švec¹¹,
Pavlyk Serhii¹²,
Oleksandr Lysytsia¹³,
Jacek Wachowiak¹⁴,
Jan Styczyński¹

¹Department of Pediatric Hematology and Oncology, Collegium Medicum, Antoni Jurasz University Hospital in Bydgoszcz, Nicolaus Copernicus University Torun, Bydgoszcz, Poland

²Department of Pediatric Hematology and Oncology, Teaching Hospital Motol, 2nd Medical School, Charles University Motol, Prague, Czech Republic

³Department of Pediatric Oncology, Faculty of Medicine, University Hospital Brno, Masaryk University, Brno, Czech Republic

⁴Department of Pediatrics, Division of Pediatric Hematology and Oncology, University Hospital Centre, Zagreb, Croatia

⁵School of Medicine, University of Zagreb, Zagreb, Croatia

⁶Department of Pediatrics, Faculty of Medicine, Clinical Hospital Center Rijeka, University of Rijeka, Rijeka, Croatia

⁷Department of Pediatric Hematology and Hemopoietic Stem Cell Transplantation, Central Hospital of Southern Pest-National Institute of Hematology and Infectious Diseases, Budapest, Hungary

⁸Center of Pediatric Oncology and Hematology, Vilnius University, Vilnius, Lithuania

⁹Fundeni Clinical Institute, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

¹⁰Department of Pediatrics, Division of Oncology and Hematology, Medical Centre Ljubljana, Ljubljana, Slovenia

¹¹Bone Marrow Transplantation Unit, Department of Pediatric Hematology and Oncology, National Institute of Children's Diseases, Comenius University, Bratislava, Slovakia

¹²Department of Children's, National Cancer Institute, Kyiv, Ukraine

¹³National Pediatric Specialized Hospital

"OHMATDYT", Kyiv, Ukraine

¹⁴Department of Pediatric Oncology, Hematology and Transplantology, Poznan University of Medical Sciences, Poznan, Poland

Abstract

Hematopoietic cell transplantation (HCT) is widely used as a treatment for acquired and congenital disorders. In recent years, a significant increase in transplant activity around the world has been observed, especially in Eastern European countries. This article aimed to assess progress and trends in pediatric HCT in Central-Eastern European countries between 2013 and 2018. Transplant activity survey in 2013 and 2018 in nine Central-Eastern European countries (Czech Republic, Croatia, Hungary, Lithuania, Poland, Romania, Slovakia, Slovenia, and Ukraine) was performed. The highest transplant rates in total were found in the Czech Republic and Hungary. When calculated per 10 million of the pediatric population, a 25.9% increase in the number of allo-HCT was observed with the highest in Croatia, Romania, Lithuania, and Poland; and a 12.2% increase in the number of auto-HCT was observed with the highest in Slovenia, Slovakia, Romania, Poland, Ukraine, and Croatia. We have shown, over the years 2013 and 2018, in some countries of Central-Eastern Europe that there was a significant increase in transplant activity, especially in those with the lower rates. This increase was observed mainly in centers already existing in 2013, especially in the allo-HCT setting. The rise of activity was significantly less influenced by the creation of new transplant centers or the increase in the number of pediatric transplant beds. In conclusion, our analysis indicates that in the Czech Republic, Hungary, Lithuania, and Slovenia, the actual infrastructure and the number of HCTs cover the needs, whereas in other countries, especially in Romania and Ukraine, the number of HCT needs to be increased.

© 2020 Polish Society of Hematology and Transfusion Medicine, Insitute of Hematology and Transfusion Medicine. Published by Sciendo. All rights reserved.

Keywords:

hematopoietic cell transplantation, children, Central-Eastern European countries

Introduction

Hematopoietic cell transplantation (HCT) is a method of treatment for many congenital and acquired hematological diseases and organ malignancies [1]. According to the European Society for Blood and Marrow Transplantation (EBMT) activity survey in 2013, a record number of 39,209 HCT in 34,809 patients performed in Europe and associated countries was reported, whereas in 2018 this number raised to 47,468 HCT in 42,901 patients [2, 3]. The EBMT activity survey has been conducted each year since 1990 [4], therefore, we can follow not only the increasing number of HCT every year but also the changing trends regarding the source of the stem cells, type of transplant, or indications for transplant procedures. Since the 2012 EBMT survey, we could observe HCT activity in pediatric transplants performed either in dedicated pediatric HCT centers or in centers performing transplants in both adult (>18 years of age at transplant) and pediatric patients [5].

In the 2014 EBMT activity survey, a significant increase in HCTs in Eastern European countries was reported for the first time [6], with the highest increase for allogeneic HCT (allo-HCT) in Romania, Russia,

Turkey, Croatia, and Serbia and autologous HCT (auto-HCT) in Romania, Serbia, and Russia as well as in Turkey and Iran [6].

The last report on survey activity (1985–2004) in pediatric HCT setting in Eastern European countries was published in 2008 [7], and to our knowledge, no other publication was done in this field. Due to observed changes in pediatric hematopoietic transplantation in Central-Eastern Europe, we have decided to analyze the progress over the past 5 years. This report is based on the data collected from an activity survey in 2013 and 2018 in nine Central-Eastern European countries (Czech Republic, Croatia, Hungary, Lithuania, Poland, Romania, Slovakia, Slovenia, and Ukraine).

The objective of this study was to assess progress and trends in pediatric HCT in Central-East European countries in the last 5 years.

Patients and methods

Design of the study

Centers coordinating pediatric HCT in Central-Eastern European countries were invited to participate in the survey on the current situation and transplant activity,

*Corresponding author: Krzysztof Czyżewski, Department of Pediatric Hematology and Oncology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Skłodowskiej-Curie 9, 85-094 Bydgoszcz, Poland, phone: +48 52 585 48 60, fax: +48 52 585 40 87, e-mail: k.czyzewski@cm.umk.pl

in the pediatric setting, as listed in table I. This report presents the results of the survey activity in 2013 and 2018.

Data collection

In November 2019, a survey on transplant activity in a pediatric setting was distributed by e-mail. The main national center collected data from other centers in the country. Collected data were sent to the coordinating center in the Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University Torun, Antoni Jurasz University Hospital in Bydgoszcz, Bydgoszcz, Poland.

There was no need for Bioethical Committee approval for this study, as no study on patients was performed. All participants of the survey are co-authors of this manuscript and have given their agreement for publication.

Pediatric population and transplant rates

The pediatric population was defined as all individuals aged from 0 to 18 years in each analyzed year. Transplant rates were calculated as a total HCT per 10 million (M) of the pediatric population in each country without correction for patients traveling to a foreign country to receive HCT. For each country, total population numbers and pediatric population numbers were obtained from Eurostat's for 2013 and 2018 (<https://ec.europa.eu/eurostat/data/database>). We considered an increase or decrease of $\pm 5\%$ as a non-relevant

change. Transplant rates were categorized as low (<100), moderate (101–200), high (201–300), and very high (>300 HCT/10 M pediatric population per year).

Results

Reporting countries

We sent a survey to Central-Eastern European countries/national coordinators. Complete data were returned from eight countries (Czech Republic, Croatia, Hungary, Lithuania, Poland, Romania, Slovakia, and Slovenia) and were analyzed (Tab. I, Fig. 1). The data received from Ukraine were not sufficient to perform a full analysis.

The Czech Republic

Czech Republic's pediatric population increased by 6.0% between 2013 and 2018 (from 1.839 M to 1.949 M). In 2013 and 2018, there were two pediatric HCT centers: in Brno specialized in auto-HCT and Prague performing both allo- and auto-HCT. The total number of pediatric transplant beds did not change in the analyzed period, however, calculated per 10 M pediatric population, the number of pediatric HCT beds was 65.2 in 2013 and 61.6 in 2018 (5.6% decrease due to population increase). An increasing trend was observed in the number of allo- and auto-HCT. A total of 30 allo-HCT were performed in 2013, while 37 in 2018 (23.3% increase). When calculated per 10 M of the pediatric population, a 16.4% increase was

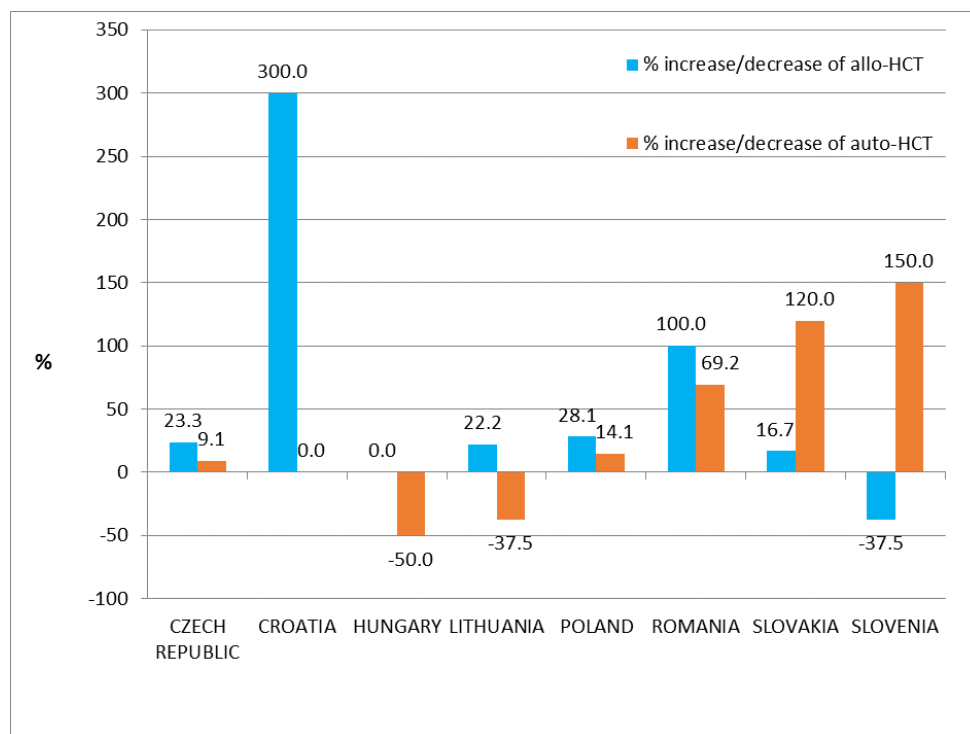


Fig. 1. Percentage of increase/decrease in HCT activity between 2013 and 2018 in reported countries (no possibility to calculate change for Ukraine)

Table I. Number of HCT in children in Central-East Europe countries in 2013 and 2018

COUNTRY	CZECH REPUBLIC			CROATIA			HUNGARY			LITHUANIA			POLAND		
	2013	2018	Change (%)	2013	2018	Change (%)	2013	2018	Change (%)	2013	2018	Change (%)	2013	2018	Change (%)
Popultion (Eurostat)[mln]	10.516	10.610	0.9	4.262	4.105	-3.7	9.908	9.778	-1.3	2.971	2.808	-5.5	38.062	37.977	-0.2
Pediatric population (Eurostat)[mln]	1.839	1.949	6.0	0.786	0.717	-8.8	1.758	1.715	-2.4	0.544	0.503	-7.5	7.005	6.874	-1.9
Number of pediatric HCT centers	2	2	0.0	2	2	0.0	2	2	0.0	1	1	0.0	5	6	20.0
Number of pediatric transplant beds	12	12	0.0	3	3	0.0	16	16	0.0	4	6	50.0	35	45	28.6
Number of allo-HCT	30	37	23.3	3	12	300.0	33	33	0.0	9	11	22.2	114	146	28.1
Number of auto-HCT	33	36	9.1	5	5	0.0	24	12	-50.0	8	5	-37.5	34	39	14.7
Total number of allo-HCT and auto-HCT	63	73	15.9	8	17	112.5	57	45	-21.1	17	16	-5.9	148	185	25.0
Number of HCT in ALL	9	12		5	4		13	4		5	2		33	60	
Number of HCT in AML	4	8		1	1		4	3		1	2		24	20	
Number of HCT in MDS	6	5		0	1		5	14		1	1		9	16	
Number of HCT in CML	1	0		0	0		0	0		0	0		2	2	
Number of HCT in NHL	0	2		0	0		4	0		1	1		8	6	
Number of HCT in HL	1	1		0	0		2	0		3	2		4	7	
Number of HCT in SAA/ BMF	1	7		1	2		2	2		1	2		15	17	
Number of HCT in NBL	12	9		4	5		6	3		2	1		20	22	
Number of HCT in Ewing sarcoma	5	4		1	0		3	4		3	2		5	6	
Number of HCT in primary immunodeficiency	7	3		1	3		3	2		0	3		21	16	
Number of HCT in metabolic disorders	2	0		0	0		1	0		0	0		0	5	
Number of pediatric HCT centers/10 mln of pediatric population	10.9	10.3	-5.6	25.4	27.9	9.7	11.4	11.7	2.5	18.4	19.9	8.1	7.1	8.7	22.3
Number of pediatric transplant beds/10 mln of pediatric population	65.2	61.6	-5.6	38.2	41.9	9.7	91.0	93.3	2.5	73.6	119.3	62.1	50.0	65.5	31.0
Number of allo-HCT/ 10 mln of pediatric population	163.1	189.9	16.4	38.2	167.4	338.7	187.8	192.4	2.5	166.5	218.7	32.1	162.7	212.4	30.5
Number of auto-HCT/ 10 mln of pediatric population	179.4	184.7	3.0	63.6	69.8	9.7	136.6	70.0	-48.8	147.1	99.4	-32.4	48.5	56.7	16.9
Total number of allo-HCT and auto-HCT/10 mln of pediatric population	342.5	374.6	9.4	101.8	237.2	133.1	324.3	262.4	-19.1	312.6	318.1	1.7	211.3	269.1	27.4

AML – acute myelogenous leukemia; ALL – acute lymphoblastic leukemia; allo-HCT – allogeneic hematopoietic cell transplantation; auto-HCT – autologous hematopoietic cell transplantation; BMF – bone marrow failure; CML – chronic myelogenous leukemia; ES – Ewing's sarcoma; HCT – hematopoietic cell transplantation; HL – Hodgkin's lymphoma; MDS – myelodysplastic syndrome; n.d. – no data; NBL – neuroblastoma; NHL – non-Hodgkin's lymphoma; PID – primary immunodeficiency; SAA – severe aplastic anemia; * – data not including Ukraine

continued Table I.

COUNTRY	ROMANIA			SLOVAKIA			SLOVENIA			UKRAINE			TOTAL		
	2013	2018	Change (%)	2013	2018	Change (%)	2013	2018	Change (%)	2013	2018	Change (%)	2013	2018	Change (%)
Popultion (Eurostat)[mln]	20.020	19.531	-2.4	5.410	5.443	0.60	2.058	2.067	0.4	45.373	42.217	-7.0	138.6	134.5	-2.9
Pediatric population (Eurostat)[mln]	3.786	3.681	-2.8	1.075	1.062	-1.2	0.356	0.366	3.0	7.990	7.609	-4.8	25.1	24.5	-2.6
Number of pediatric HCT centers	2	2	0.0	1	1	0.0	1	1	0.0	3	3	0.0	19	20	5.3
Number of pediatric transplant beds	9	11	22.2	6	6	0.0	2	2	0.0	9	11	22.2	96	112	16.7
Number of allo-HCT	9	18	100.0	12	14	16.7	8	5	-37.5	21	17	-19.0	239	293	22.6
Number of auto-HCT	13	22	69.2	5	11	120.0	2	5	150.0	39	43	10.2	163	178	9.2
Total number of allo-HCT and auto-HCT	22	40	81.8	17	25	47.1	10	10	0.0	60	60	0	402	471	17.2
Number of HCT in ALL	2	6		4	6		2	4		n.d.	4		73*	98*	34.2*
Number of HCT in AML	4	3		3	2		2	0		n.d.	3		43*	39*	-9.3*
Number of HCT in MDS	0	2		0	2		0	0		n.d.	1		21*	41*	95.2*
Number of HCT in CML	1	0		0	0		0	0		n.d.	0		4*	2*	-50.0*
Number of HCT in NHL	2	0		0	0		0	0		n.d.	2		15*	9*	-40.0*
Number of HCT in HL	5	10		0	0		0	0		n.d.	2		15*	20*	33.3*
Number of HCT in SAA/ BMF	2	4		1	1		2	0		n.d.	3		25*	35*	40.0*
Number of HCT in NBL	5	12		3	8		1	2		10	28		63	90	42.9
Number of HCT in Ewing sarcoma	1	2		1	0		1	0		5	10		25	28	12
Number of HCT in primary immunodeficiency	0	1		3	1		1	1		n.d.	2		36*	30*	-16.7*
Number of HCT in metabolic disorders	0	0		1	0		1	0		n.d.	0		5*	5*	0.0*
Number of pediatric HCT centers/10 mln of pediatric population	5.3	5.4	2.9	9.3	9.4	1.2	28.1	27.3	-2.9	3.7	3.9	5.0	7.6	8.2	8.1
Number of pediatric transplant beds/10 mln of pediatric population	23.8	29.9	25.7	55.8	56.5	1.2	56.2	54.6	-2.9	11.3	14.4	28.3	38.2	45.8	19.8
Number of allo-HCT/10 mln of pediatric population	23.8	48.9	105.7	111.6	131.7	18.0	224.7	136.4	-39.3	26.3	22.3	-15.0	95.1	119.7	25.9
Number of auto-HCT/10 mln of pediatric population	34.3	59.8	74.1	46.5	103.5	122.6	56.2	136.4	142.8	48.8	56.5	15.8	64.8	72.7	12.2
Total number of allo-HCT and auto-HCT/10 mln of pediatric population	58.1	108.7	87.0	158.1	235.2	48.8	280.9	272.8	-2.9	75.1	78.9	5.0	159.9	192.4	20.3

AML – acute myelogenous leukemia; ALL – acute lymphoblastic leukemia; allo-HCT – allogeneic hematopoietic cell transplantation; auto-HCT – autologous hematopoietic cell transplantation; BMF – bone marrow failure; CML – chronic myelogenous leukemia; ES – Ewing's sarcoma; HCT – hematopoietic cell transplantation; HL – Hodgkin's lymphoma; MDS – myelodysplastic syndrome; n.d. – no data; NBL – neuroblastoma; NHL – non-Hodgkin's lymphoma; PID – primary immunodeficiency; SAA – severe aplastic anemia; * – data not including Ukraine

observed (from 163.1 allo-HCT per 10 M pediatric population in 2013 to 189.9 allo-HCT per 10 M pediatric population in 2018). A total of 33 auto-HCT were performed in 2013, while 36 in 2018 (9.1% increase). When calculated for 10 M of the pediatric population, an insignificant 3.0% increase was observed (from 179 auto-HCT per 10 M pediatric population to 185 auto-HCT per 10 M pediatric population). The total number of auto- and allo-HCT calculated per 10 M pediatric population increased from 342.5 in 2013 to 374.6 in 2018 (9.4% increase).

The main indication for allo-HCT was acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), while neuroblastoma (NBL) and Ewing's sarcoma (ES) for auto-HCT, both in 2013 and 2018. In 2013, one patient was transplanted due to chronic myelogenous leukemia (CML) and none in 2018. A significant increase (600.0%) of allo-HCT was observed in severe aplastic anemia (SAA) and bone marrow failure (BMF) (one in 2013 and seven in 2018). Besides natural fluctuations in annual disease incidence, this may reflect a change in the indications toward frontline HCT using rapidly available matched unrelated donors instead of primary immunosuppressive therapy.

As early as 2013, the Czech Republic was among the countries with a very high transplant rate per 10 M of the pediatric population (the highest number of HCTs per 10 M of pediatric population, among analyzed countries). We assume that the number of centers, pediatric beds, and transplants covers current country needs.

Croatia

Croatian pediatric population decreased from 0.786 M children in 2013 to 0.717 M in 2018 (8.8% decrease). There are two HCT centers performing transplantation in children, both in Zagreb: one joint adult-pediatric center performing allo- and auto-HCT, and the other performing only auto-HCT for children. The total number of pediatric transplant beds is three. Both, the number of pediatric transplant centers and beds did not change between 2013 and 2018. Calculated per 10 M pediatric population, the number of pediatric HCT beds was 38.2 in 2013 and 41.9 in 2018, respectively (the observed increase is caused by the decrease in the pediatric population). An increasing trend was observed in the number of allo-HCT from 3 in 2013 to 12 transplants in 2018 (i.e., an increase of 300.0%). Calculated per 10 M of the pediatric population, an increase of 338.7% was observed (from 38 to 167 transplants per 10 M of the pediatric population). Although the number of autologous transplants in 2013 and 2018 is the same (five transplants/year), there is a 9.7% increase in the number of auto-HCT per 10 M of the pediatric population (from 63.6 to 69.8 transplants per 10 M pediatric population) due to decrease of the pediatric population. The total number of auto- and allo-HCT calculated per 10 M pediatric population has increased from 101.8 in 2013 to 237.2 in 2018 (133.1% increase).

The main indication for allo-HCT was ALL and high-risk NBL for auto-HCT, both in 2013 and 2018. More patients were transplanted in 2018 due to SAA, BMF, and primary immunodeficiency (PID) compared to 2013. No patient was transplanted due to CML.

Despite an observed increase, the number of transplants per 10 M of the pediatric population in both 2013 and 2018 has shifted Croatia from the group of countries with a moderate number of transplants (101–200 transplants per 10 M of the pediatric population/year) in

2013 to a high number of transplants (201–300 transplantations per 10 M pediatric population/year) in 2018. We could expect a further increase in the number of transplants in subsequent years.

Hungary

Hungarian pediatric population insignificantly decreased by 2.4% between 2013 and 2018 (from 1.758 M to 1.715 M). In 2013 and 2018, there were two pediatric HCT centers (Budapest and Miskolc) performing allo- and auto-HCT in children. The total number of pediatric transplant beds did not change between 2013 and 2018 (16 beds). Calculated per 10 M pediatric population, the number of pediatric HCT beds was 91.0 in 2013 and 93.3 in 2018 (insignificant 2.5% increase due to population decrease). The number of allo-HCT did not change in 2013 and 2018 (33 allo-HCT/year). The calculated ratio for 10 M of the pediatric population did not change (187.8 in 2013 and 192.4 in 2018 representing 2.4% insignificant increase due to population decrease). Significantly, a 50.0% decrease was observed in the case of auto-HCT (from 24 in 2013 to 12 in 2018). When calculated for 10 M of the pediatric population, a 48.8% decrease was observed (from 136.6 auto-HCT per 10 M pediatric population in 2013 to 70.0 auto-HCT per 10 M pediatric population in 2018). The total number of auto- and allo-HCT calculated per 10 M pediatric population decreased from 324.3 in 2013 to 262.4 in 2018 (19.1% decrease).

The main indication for allo-HCT was ALL in 2013 and myelodysplastic syndrome (MDS) in 2018, while NBL and ES for auto-HCT in 2013 and 2018. There was a significant decrease in the number of HCT in ALL and NBL patients (decrease from 13 in 2013 to 4 in 2018 in ALL and decrease from 6 in 2013 to 3 in 2018 in NBL). No HCT due to CML was performed in 2013 and 2018, while the number of transplantations due to SAA/BMF did not change (two transplantations/year).

Our analysis indicates that in 2013, Hungary was among the countries with a very high transplant rate per 10 M of the pediatric population. Most probably the number of centers, pediatric beds, and the number of transplants cover current country needs.

The observed decrease in 2018 in the number of transplants is probably due to periodic fluctuations in the number of cases, especially ALL being the main pediatric indication for allo-HCT.

Lithuania

Lithuanian pediatric population decreased by 7.5% between 2013 and 2018 (from 0.544 M to 0.503 M). In 2013 and 2018, there was one pediatric HCT center in Vilnius performing allo- and auto-HCT. The number of pediatric HCT beds increased from 4 in 2013 to 6 beds in 2018 (50.0% increase). Calculated per 10 M pediatric population, the number of pediatric HCT beds was 73.6 in 2013 and 119.3 in 2018 (62.1% increase due to an increase in the number of beds and decrease of the pediatric population). An increasing trend was observed in the number of allo-HCT from 9 in 2013 to 11 in 2018 (22.2% increase). The calculated ratio of allo-HCT for 10 M of the pediatric population increased from 165.5 in 2013 to 218.7 in 2018 (32.1% increase). A decrease of 37.5% was observed in auto-HCT, from 8 in 2013 to 5 in 2018. When calculated for 10 M of the pediatric population, a 32.4% decrease in auto-HCT was observed

(from 147.1 in 2013 to 99.4 in 2018). The total number of auto-HCT and allo-HCT calculated per 10 M pediatric population did not change (312.6 in 2013 and 318.1 in 2018; 1.7% insignificant increase).

The main indication for HCT in 2013 was ALL, Hodgkin lymphoma (HL), and ES. In 2018, less HCT was performed in patients with ALL, HL, ES, and NBL, while more due to PID. No transplantations were performed due to CML in 2013 and 2018, while one HCT was performed due to SAA/BFM in 2013 and two in 2018.

In 2013, Lithuania was among the countries with a very high transplant rate per 10 M of the pediatric population. In addition, in 2018 two more pediatric transplant beds were available (the highest number of transplant beds per 10 M of pediatric population, among analyzed countries). We assume that the number of pediatric beds and the number of transplants cover the needs. However, it should be noted that the Vilnius center also performs transplants for children from Latvia for standard indications except PID.

Poland

Polish pediatric population has not changed significantly between 2013 and 2018 (7.005 M in 2013 and 6.874 M in 2018; -1.9%). In 2013, there were five pediatric HCT centers (Bydgoszcz, Poznan, Krakow, Lublin, and Wroclaw) performing auto- and allo-HCT. In 2015, the center in Wroclaw moved to a new location with the simultaneous increase of pediatric transplant beds (five new beds). In 2018, a new pediatric HCT center was established in Warsaw with five pediatric beds. Therefore, in 2018, six pediatric HCT centers were active in Poland (five performing allo- and auto-HCT; one performing auto-HCT). The total number of pediatric transplant beds increased from 35 in 2013 to 45 in 2018 (28.6% increase). Calculated per 10 M of the pediatric population, the number of pediatric HCT beds increased from 50.0 in 2013 to 65.5 in 2018 (31.0% increase). An increasing trend was also observed in the number of allo- and auto-HCT. A total of 114 allo-HCT were performed in 2013, while 146 in 2018 (28.1% increase). When calculated per 10 M of the pediatric population, a 30.5% increase was observed (from 162.7 allo-HCT per 10 M of the pediatric population to 212.4 allo-HCT per 10 M pediatric population). In the case of auto-HCT, 34 procedures were performed in 2013, while 39 in 2018 (14.7% increase). When calculated for 10 M of the pediatric population, a 16.9% increase was observed (from 48.5 auto-HCT per 10 M pediatric population to 56.7 auto-HCT per 10 M pediatric population). The total number of auto- and allo-HCT calculated per 10 M pediatric population increased from 211.3 in 2013 to 269.1 in 2018 (27.4% increase).

The main indication for allo-HCT was ALL and AML, while NBL for auto-HCT, both in 2013 and 2018. Both in 2013 and 2018, two transplantations due to CML were performed yearly. SAA/BMF was an indication for 15 allo-HCT in 2013 and 17 allo-HCT in 2018.

A significant increase in the number of pediatric transplant beds and the number of HCT in Poland was observed in analyzed years. Despite an observed increase, the number of HCT per 10 M of the pediatric population in both 2013 and 2018 ranks Poland in a group of countries with a high number of transplants (201–300 transplants per 10 M of the pediatric population). We expect a further increase in the number of transplants. Probably the number of centers, pediatric beds, and transplants still does not completely cover the country's needs.

Romania

Romanian pediatric population has not changed significantly between 2013 and 2018 (3.786 M in 2013 to 3.681 M in 2018; -2.8%). Between 2013 and 2018, the number of HCT centers performing allo- and auto-HCT did not change as there were two centers: one in Bucharest (pediatric only) and one in Timisoara (joint adult-pediatric center) performing allo- and auto-HCT. The total number of pediatric transplant beds increased from 9 in 2013 to 11 in 2018 (22.2% increase). Calculated per 10 M pediatric population, the number of beds increased from 23.8 in 2013 to 29.9 in 2018 (25.7% increase). A significant increase was observed in the number of allo- and auto-HCT. Nine allo-HCT were performed in 2013, while 18 in 2018 (100.0% increase). When calculated per 10 M of the pediatric population, a 105.7% increase was observed (from 23.8 allo-HCT per 10 M pediatric population to 48.9 allo-HCT per 10 M of the pediatric population). In the case of auto-HCT, 13 procedures were performed in 2013, while 22 in 2018 (69.2% increase). When calculated for 10 M of the pediatric population, a 74.1% increase was observed (from 34.3 auto-HCT per 10 M of the pediatric population to 59.8 auto-HCT per 10 M of the pediatric population). The total number of auto- and allo-HCT calculated per 10 M pediatric population increased from 58.1 in 2013 to 108.7 in 2018 (87.0% increase).

In 2013, the main indication for allo-HCT was AML, while NBL and HL for auto-HCT. In 2018, the main indication for allo-HCT was ALL (a significant increase from 2 to 6 procedures) and AML, while NBL and HL for auto-HCT (a significant increase from 5 to 12 procedures for NBL and increase from 5 to 10 procedures for HL). One allo-HCT was performed due to CML in 2013, while none in 2018. SAA/BMF was an indication for two allo-HCT in 2013 and four allo-HCT in 2018. A significant increase in the number of beds and number of HCT has been observed in analyzed years. Despite an observed increase, the number of transplants per 10 M of the pediatric population in both 2013 and 2018 shifted Romania from the group of countries with a low number of transplants (1–100 transplants per 10 M of the pediatric population) to a moderate number of transplants (101–200 transplantations per 10 M pediatric population). Our data suggest that the number of pediatric beds and the number of transplants do not cover country needs, and we expect a significant increase in the number in allo- and auto-HCT.

Slovakia

The Slovakian pediatric population has not changed significantly between 2013 and 2018 (1.075 M in 2013 to 1.062 M in 2018; -1.2%). Between 2013 and 2018, there was one pediatric HCT center performing both auto- and allo-HCT, located in Bratislava. The total number of pediatric transplant beds did not change in analyzed years, as there were six pediatric HCT beds. Calculated per 10 M of the pediatric population, the number of beds also did not change (55.8 in 2013 and 56.5 in 2018; 1.2% decrease due to pediatric population decrease). A significant increase was observed in the number of allo- and auto-HCT. Twelve allo-HCT were performed in 2013, while 14 in 2018 (16.7% increase). When calculated per 10 M of the pediatric population, an 18.0% increase was observed (from 111.6 allo-HCT per 10 M of the pediatric population to 131.7 allo-

HCT per 10 M of the pediatric population). In the case of auto-HCT, 5 procedures were performed in 2013, while 11 in 2018 (120.0% increase). When calculated for 10 M of the pediatric population, a 122.6% increase was observed (from 46.5 auto-HCT per 10 M of the pediatric population to 103.5 auto-HCT per 10 M of the pediatric population). The total number of auto- and allo-HCT calculated per 10 M pediatric population increased from 158.1 in 2013 to 235.2 in 2018 (48.8% increase).

In 2013, the main indication for allo-HCT was ALL, AML, and PID, while NBL for auto-HCT. In 2018, the main indication for allo-HCT was ALL, AML, and MDS, while NBL for auto-HCT (a significant increase from 3 to 8 procedures). One allo-HCT was performed due to SAA/BMF in 2013 and 2018 while none due to CML.

No changes were observed in the number of pediatric HCT beds. Despite an observed increase in the number of transplants per 10 M of the pediatric population in both 2013 and 2018 shifted Slovakia from the group of countries with a moderate number of transplants (101–200 transplantations per 10 M of the pediatric population) to a high number of transplants (201–300 transplants per 10 M of the pediatric population). We expect a further increase in the number of transplants. Probably the number of centers, pediatric beds, and transplants does not cover the country's needs.

Slovenia

Slovenian pediatric population has not changed significantly between 2013 and 2018 (0.356 M and 0.366 M respectively; 3.0% insignificant increase). There is one joint adult-pediatric center performing allo- and auto-HCT in children (Ljubljana). The total number of pediatric HCT beds did not change (two beds). When calculated per 10 M pediatric population, it was 56.2 in 2013 and 54.6 in 2018 (2.9 insignificant decrease due to population increase). A decrease of 37.5% for allo-HCT was observed between 2013 (8 procedures) and 2018 (5 procedures). When calculated per 10 M of the pediatric population, it was 39.3% decrease (from 224.7 allo-HCT per 10 M pediatric population to 136.4 allo-HCT per 10 M pediatric population). In the case of auto-HCT, a significant (150.0%) increase was observed (from 2 procedures in 2013 to 5 procedures in 2018). When calculated per 10 M of the pediatric population, a 142.8% increase was observed (from 56.2 auto-HCT per 10 M pediatric population to 136.4 auto-HCT per 10 M pediatric population). The total number of auto- and allo-HCT calculated per 10 M pediatric population insignificantly decreased from 280.9 in 2013 to 272.8 in 2018 (2.9%). In 2013, the main indication for allo-HCT was ALL, AML, and SAA/BMF (two procedures each), and one transplantation was performed for PID and metabolic disorder, respectively. In the case of auto-HCT, one procedure was performed due to NBL and one due to ES. In 2018, four transplantations were performed due to ALL and one due to PID, while four auto-HCT due to NBL and three auto-HCT (not shown in the table as another indication) due to other solid tumors. No procedures due to CML were performed in 2013 and 2018. In 2018, there were no transplantations in SAA/BMF patients.

The number of pediatric transplant beds and the number of transplantations in Slovenia did not change. The number of transplants per 10 M pediatric population in both 2013 and 2018 ranks

Slovenia in a group of countries with a high number of transplants (201–300 transplants per 10 M of the pediatric population), taking into consideration a small pediatric population, we think that one center, the number of pediatric beds and the number of transplants cover the country needs at present time. However, due to the global upward trend in transplant activity, the number of transplant beds may need to be increased in the near future.

Ukraine

Ukrainian pediatric population insignificantly decreased from 7.990 M in 2013 to 7.609 M in 2018 (4.8% decrease). According to the obtained data, a complete analysis was not possible. Between 2013 and 2018, the number of HCT centers performing allo- and auto-HCT did not change – there were three centers in Kyiv: only one pediatric and two joint adult-pediatric centers performing allo- and auto-HCT. Allo-HCT from unrelated donors is not performed in Ukraine and patients are transplanted in foreign countries (Belorussia, Italy, Israel, Poland, and Turkey). The total number of pediatric transplant beds increased from 9 in 2013 to 11 in 2018 (22.2% increase). Calculated per 10 M of the pediatric population, the number of pediatric HCT beds increased from 11.3 in 2013 to 14.4 in 2018 (28.3% increase). A decrease of 19.0% for allo-HCT was observed between 2013 (21 procedures) and 2018 (17 procedures). When calculated per 10 M of the pediatric population, it was a 15.0% decrease (from 26.3 allo-HCT per 10 M pediatric population to 22.3 allo-HCT per 10 M pediatric population). In the case of auto-HCT, a 10.3% increase was observed (from 39 procedures in 2013 to 43 procedures in 2018). When calculated per 10 M of the pediatric population, a 15.8% increase was observed (from 48.8 auto-HCT per 10 M of the pediatric population to 56.5 auto-HCT per 10 M of the pediatric population). The total number of auto-HCT and allo-HCT calculated per 10 M pediatric population increased from 75.1 in 2013 to 78.9 in 2018 (5.0%), but it was connected with a 4.8% pediatric population decrease. It ranking Ukraine to countries with a low number of transplantations (1–100 HCT per 10 M of the pediatric population).

In 2018, the rate of auto-HCT per 10 M of pediatric population (56.5) was close to respective rates in Croatia (69.8), Hungary (70.0), Romania (59.8), and Poland (56.7) and significantly lower than in Czech Republic (184.7), Slovenia (136.4), and Slovakia (103.5). In the case of allo-HCT in 2018, the rate per 10 M of the pediatric population was very significantly lower (22.3) than in other countries (Romania -48.9; Lithuania -218.7) confirming deficiency in the allo-HCT setting. It was also seen in the migration of Ukrainian patients to other countries for allo-HCT from unrelated donors.

Summary

Over the past 5 years, the total number of pediatric transplant centers increased by one (in Poland) in nine studied countries (Czech Republic, Croatia, Hungary, Lithuania, Poland, Romania, Slovakia, Slovenia, and Ukraine). During this period, the number of beds increased from 96 to 112 (16.7%): Lithuania (50% increase, 2 beds), Poland (28.6% increase, 10 beds), Romania (22.2% increase, 2

beds), and Ukraine (22.2% increase, 2 beds). Calculated per 10 M of the pediatric population, an increase in allo-HCT was observed from 95.1 to 119.7 (25.9% increase), highest in Croatia (+338.7%), Romania (+105.7%), Lithuania (+32.1%), and Poland (+30.5%). Calculated per 10 M of pediatric population, a significantly lower increase in the number of auto-HCT was observed in analyzed countries: from 64.8 to 72.7 (12.2% increase), highest in Slovenia (142.8% increase), Slovakia (122.5% increase), Romania (74.1% increase), Poland (16.9% increase), Ukraine (15.8% increase), and Croatia (9.7% increase). Analyzing the total of auto- and allo-HCTs, an increase of 20.3% was observed (from 159.9 in 2013 to 192.4 per 10 M of the pediatric population in 2018). The largest increase was observed in Croatia (+133.1%), Romania (+87.0%), Slovakia (+48.8%), and Poland (+27.4%), followed by Czech Republic (+9.4%) and Ukraine (+5.0%). A decrease was observed in Hungary (-19.1%), and no change in Lithuania and Slovenia (Fig. 2).

Discussion

This is the first report that demonstrates the development of HCT activity in Central-East European countries in the pediatric population in two-time points (2013 and 2018). The EBMT activity surveys conducted since 1990 indicate a steady increase in the number of HCT, which exceeded 47,000 transplantations per year in 2018 [3, 8]. This expansion is much more pronounced in allo-HCT (7.1% in 2018 when compared to 2017) setting than in the auto-HCT setting (2.4% in 2018 when compared to 2017), especially in the pediatric

population (9.4% allo-HCT vs. 3.0% auto-HCT) [3]. When compared to 2003 and 2013 activity reports, our analysis shows a significant increase in transplant activity in the pediatric population in Central-East European countries in 2018, especially in the allo-HCT setting [2, 3, 7].

Compared to 2013, we observed an increase in the number of transplants due to ALL, MDS, HL, and SAA/BFM in 2018, which was also observed in other countries in respective indications [2, 3]. The number of transplants due to NBL also increased, while metabolic diseases were at the same level. However, a significant decrease in the number of pediatric transplants was observed due to non-HL when compared to data from the 2013 and 2018 annual activity surveys in the general population [2], probably due to the development of the targeted therapy. The introduction of tyrosine kinase inhibitors has marked a revolutionary step in CML patients resulting in the low number of transplants when compared with previous activity reports [2, 3, 9].

Our analysis suggests that in the Czech Republic, Hungary, Lithuania, and Slovenia the infrastructure and the number of HCT cover the needs. In other countries, especially in Romania and Ukraine, the number of HCT per 10 M of the pediatric population is lower and there is a real need for the increase.

In the last EBMT activity survey report [3], the most impressive growth was observed in hematopoietic cellular therapies, especially in the use of CAR-T. Probably in the future, the new cellular therapies will cause a further increase for pediatric transplant beds and aggravate their shortage in countries with the lowest rates.

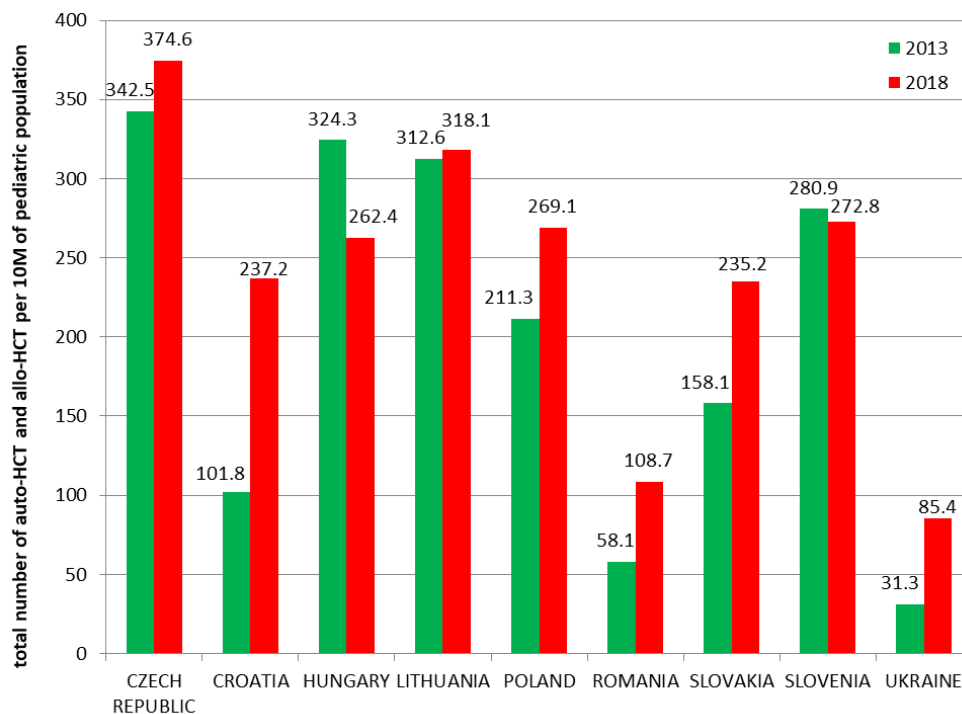


Fig. 2. The total number of auto-HCT and allo-HCT per 10M pediatric population in reported countries in 2013 and 2018

Conclusions

We have shown, over the years 2013 and 2018, in some countries of Central-Eastern Europe that there was a significant increase in transplant activity, especially in those with the lower rates. This increase is associated with an increase of transplant activity in centers already existing in 2013, especially in the allo-HCT setting. The rise of activity was significantly less influenced by the creation of new transplant centers or the increase in the number of pediatric transplant beds. Our analysis indicates that in Czech Republic, Hungary, Lithuania, and Slovenia the infrastructure and the number of HCT cover the needs, whereas in other countries, especially in Romania and Ukraine, the number of HCT and infrastructure are in a real need for the increase.

Authors' contributions

KC, JS – study design, administrative support. KC – data analysis, manuscript writing. All authors – provision of important clinical data, data check-up and final approval of the manuscript.

Conflict of interest

All authors declared no conflict of interest related to this study.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

References

- [1] Duarte RF, Labopin M, Bader P, et al. Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. *Bone Marrow Transplant* 2019;54:1525–52.
- [2] Passweg JR, Baldomero H, Bader P, et al. Hematopoietic SCT in Europe 2013: recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants. *Bone Marrow Transplant* 2015;50:476–82.
- [3] Passweg JR, Baldomero H, Chabannon C, et al. The EBMT activity survey on hematopoietic-cell transplantation and cellular therapy 2018: CAR-T's come into focus. *Bone Marrow Transplant* 2020;55:1604–1613.
- [4] Gratwohl A, Hermans J, Barrett AJ, et al. Allogeneic bone marrow transplantation for leukemia in Europe: regional differences. Report from the Leukemia Working party of the European Group for Bone Marrow Transplantation. *Bone Marrow Transplant* 1990;5:159–65.
- [5] Passweg JR, Baldomero H, Peters C, et al. Hematopoietic SCT in Europe: data and trends in 2012 with special consideration of pediatric transplantation. *Bone Marrow Transplant* 2014;49:744–50.
- [6] Passweg JR, Baldomero H, Bader P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. *Bone Marrow Transplant* 2016;51:786–92.
- [7] Wachowiak J, Labopin M, Miano M, et al. Haematopoietic stem cell transplantation in children in eastern European countries 1985–2004: development, recent activity and role of the EBMT/ESH Outreach Programme. *Bone Marrow Transplantation* 2008;41:S112–7.
- [8] Gratwohl A. Bone marrow transplantation activity in Europe 1990. European Group for Bone Marrow Transplantation (EBMT). *Bone Marrow Transplant* 1991;8:197–201.
- [9] Suttorp M, Schulze P, Glauche I, et al. Front-line imatinib treatment in children and adolescents with chronic myeloid leukemia: results from a phase III trial. *Leukemia* 2018;32:1657–69.