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STATUS OF IMMUNITY FOR VACCINE – PREVENTABLE DISEASES IN CHILDREN AFTER HEMATOPOIETIC STEM CELLS TRANSPLANTATION

OCENA ODPORNOŚCI NA CHOROBY ZWALCZANE DROGĄ SZCZEPIEŃ WŚRÓD DZIECI PO PRZESZCZEPIENIU SZPIKU

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STRESZCZENIE

Wprowadzenie: U pacjentów po transplantacji szpiku zanika pamięć immunologiczna nabyta w ciągu całego życia. Tym samym wzrasta u nich ryzyko zakażenia drobnoustrojami, takimi jak *Haemophilus influenzae, Streptococcus pneumoniae* oraz innymi. Jednakże wielu zakażeniom można zapobiegać poprzez stosowanie szczepień. Dlatego też wszyscy pacjenci po przeszczepieniu szpiku powinni być poddani ponownemu szczepieniu. Prowadzenie szczepień wśród osób po transplantacji szpiku nadal jest tematem, któremu nie poświęca się dostatecznej uwagi. Szczególnie zauważalne jest to w krajach, w których nie opracowano ogólnokrajowych standardów stosowania szczepień oraz nie ustanowiono odpowiednich regulacji w systemie ochrony zdrowia.

Cel: W pracy oceniono stan zaszczepienia przed transplantacją oraz utrzymywanie się specyficznych dla danej szczepionki przeciwciał po transplantacji szpiku.

Materiał i metody: Analizie poddano grupę liczącą 38 dzieci po przeszczepie szpiku, w tym 19 po przeszczepieniu autologicznym i 19 po przeszczepieniu allogenicznym.

Wyniki: Jedynie kilkoro spośród badanych dzieci ukończyło standardowy schemat szczepień przed transplantacją. Po średnim czasie wynoszącym 29 miesięcy (przedział: 6-67) po przeszczepieniu autologicznym i 13 miesięcy (przedział: 8-33) po przeszczepieniu allogenicznym, gdy rozpoczęto rewakcynację, u większości dzieci zaobserwowano niższy poziom przeciwciał w porównaniu z minimalnym poziomem jaki zapewniałby ochronę i wynosił średnio: 82% przeciw tężcowi, 71% przeciw Hib i ospie, 46% przeciw HBV i 38% przeciw błonicy.

Wnioski: Wszystkie osoby po transplantacji szpiku powinny podlegać szczepieniom celem stymulacji odporności na choroby, którym można zapobiegać drogą szczepień.

Słowa kluczowe*: transplantacja szpiku, szczepienia, odporność, dzieci*

ABSTRACT

Introduction: patients treated with hematopoietic stem cell transplantation (HSCT) lose immune memory accumulated through a lifetime. They are at increased risk of developing infections with microorganisms such as *Haemophilus influenza, Streptococcus pneumoniae* and others for which vaccines are available. Therefore, all patients after HSCT should be routinely revaccinated. Systemic reimmunization after HSCT is a relatively neglected area especially in countries which have not national recommendations and there is lack of systemic regulations in health care system. Objective: the rate of immunization before transplantation and the persistence of vaccine-specific antibodies after HSCT was assessed. Study design: a group of 38 children after stem cell transplantation (19 autologous, 19 allogeneic) was studied. Results: only a few patients completed standard vaccination protocol before HSCT. At the median time of 29 (range: 6-67) months after autologous and 13 (range: 8 – 33) months after allogeneic HSCT, when the revaccination was commenced, the majority of children had concentration of antibody lower than the minimum protective thresholds. That was 82% for tetanus, 71% for Hib and varicella, 46% for HBV and 38% for diphtheria. Conclusions: all HSCT recipients should be routinely revaccinated to stimulate the immunity to the vaccine-preventable diseases.

Key words: *hematopoietic stem cells transplantation, vaccination, immunity, children*

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is an established mode of therapy for a number of malignant and nonmalignant conditions (1). Substantial progress has been made in the field of HSCT during the past 40 years. Despite these advances, infectious complications constitute the major cause of morbidity, re-hospitalization and mortality after successful HSCT. There are several risk factors for infection that still exist in transplanted patients (2, 3). Impairment of humoral and cell-mediated immunity is seen in almost all HSCT recipients. The degree of immunodeficiency is determined by many factors. Reconstitution of immune system after HSCT occurs over a period of months to years (2, 4). Immune response to antigens is low and the risk of infectious complications is high during immune reconstitution. The restoration of humoral immunity for vaccine-preventable diseases in the autologous setting and the transfer of donor immunity for vaccine preventable diseases in the allogeneic setting are both limited. Moreover, the recipients usually lose immune memory of exposure to infectious agents and vaccines accumulated throughout their lives and antibody titers to vaccine preventable disease decline after HSCT. Several studies have demonstrated low levels of immunity against, measles, mumps, rubella, poliovirus, tetanus, *Streptococcus pneumoniae,* hepatitis A virus and others (5). Additionally, especially in children, serious disease finally treated with HSCT discontinue basic vaccination program. Therefore after HSCT they have none or below protective level of immunity for vaccine-preventable diseases.

The objectives of our study were to evaluate the rate of immunization before transplantation and the persistence of vaccine-specific antibodies after HSCT before start of revaccination protocol.

PATIENTS AND METHODS

Thirty-eight children (16 girls and 22 boys) treated by high-dose chemotherapy with autologous (19) and allogeneic (19; 14 from sibling and 5 from unrelated donors) HSCT were recruited to the study in years 2007-2010. Clinical details of patients are presented in table I. The indication to high-dose chemotherapy followed by autologous transplantation were: Ewing sarcoma (7), neuroblastoma (7), medulloblastoma (2), non-Hodgkin lymphoma (2) and yolk sack tumor (1). The patients were eligible for allogeneic transplantation because of poor prognosis in course of different malignant and non-malignant diseases: acute lymphoblastic leukemia (10), severe aplastic anemia (3), chronic granulomatous disease (2), severe combined immunodeficiency (1), juvenile mielomonoblastic leukemia (1), high-IgM syndrome (1) and Fanconi anemia (1).

Tab. I. Clinical characteristic
Tab. I. Charakterystyka kliniczna

	HSCT		
	all	allogeneic	autologous
number of patients	38	19	19
Gender			
male	22	12	10
female	16	7	9
age at diagnosis of primary disease (year)			
mean	7.0	5.7	8.4
median	6.3	4.2	9.8
min	0.2	0.2	1.7
max	17.5	16.8	17.5
age at HSCT (year)			
mean	8.6	7.8	9.4
median	8.5	7.2	10.4
min	0.5	0.5	2.4
max	18.7	17.3	18.7
age at revaccination (year)			
mean	10.5	9.1	11.8
median	9.8	7.9	13.6
min	1.2	1.2	3.6
max	22.3	18.3	22.3

Patients were commenced revaccination if they met inclusion criteria like as: at least 9 months after HSCT, good clinical condition, stable engraftment (ANC>1000/µl, platelet count >50000/µl), no symptoms of active infection, no symptoms of active GvHD, no treatment with immunosupresant. Informed consent was obtained from the patients or their parents. Vaccination protocol used was based on the European Blood and Marrow Transplantation group (EBMT), the Centers for Disease Control and Prevention (CDC) international guidelines for vaccination of HSCT recipients as well as personal experience (6, 7, 8, 9).

Specific vaccination history was obtained from parents and/or the individual vaccination book. The survey questions captured information, included the type, number, and schedule of specified vaccines executed before transplantation. Information collected was separated by autologous (A) and allogeneic (B) source of HSCT. Blood samples (5-10 ml) for serological testing were collected on the day that revaccination was started. Usually, blood samples were obtained at the same time that specimens were collected for routine blood tests. Blood was centrifuged, and serum was separated and frozen in aliquots at -20^{0}C on the same day, until the samples were tested in batches.

The concentration of antibody for the following antigens: hepatitis B virus (HBV), *Heamophilus influenza* type b (Hib), tetanus (T), diphtheria (D) and varicella (V) were tested using commercial enzyme linked immunosorbent assay (ELISA) kits according to the instructions of the manufacturer: ETI-AB-AUK-3 anti-HBs (DiaSorin, Italy), VaccZyme^{TM}Hib IgG (The Binding Site, UK), Tetanus and Diphtheria IgG ELISA and VZV IgG/IgM ELISA (Genzyme Vitotech GmbH, Germany).

STATISTICAL ANALYSIS

Means, medians, ranges and percentages were reported. The results of antibody concentration was compared between the two groups (allogeneic and autologous HSCT) at the time of revaccination commenced using the Yates' χ^2 or Fisher exact test. All statistical analysis were done using STATISTICA 9.0 with licence for Jagiellonian University.

RESULTS

The schedule of obligatory vaccination in Poland, which should be performed in presented group of children before HSCT was changed in years and is presented in tables II and III (10,11).

Tab. II. Obligatory in Poland since 1991 vaccination schedule

Tab. II. Obowiązujący w Polsce od 1991r. kalendarz szczepień

Age period	Vaccine	Number of doses
1-year	HBV	4
	BCG	1-2
	Dt-Tt-P	3
	La-PV	3
2-year	Measles	1
	Dt-Tt-P	1
	La-PV	1
6-year	Dt-Tt	1
	La-PV	1
7-year	BCG	1
9-year	Measles	1
11-year	La-PV	1
12-year	BCG	1
13-year-girls	Rubella	1
14-year	Dt-Tt	1

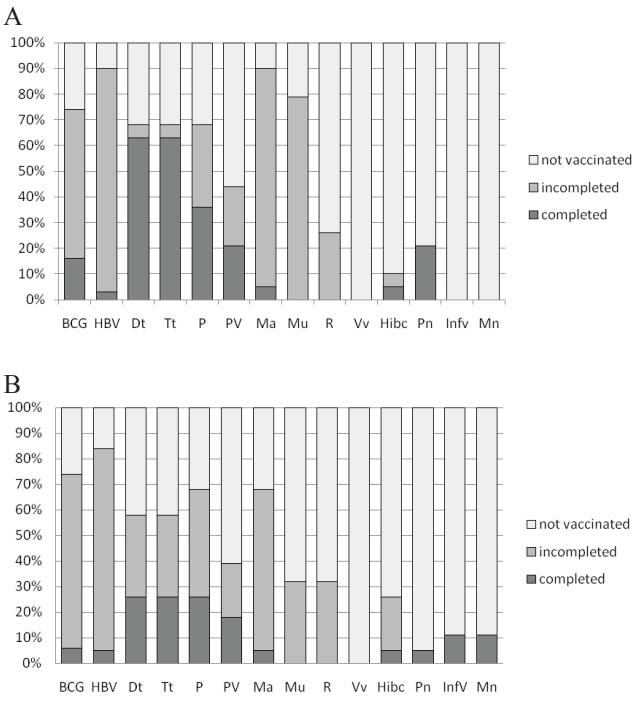
HBV - hepatitis B virus, BCG – tuberculosis, Dt – diphtheria toxoid, Tt – tetanus toxoid, P – pertussis, La-PV - live-attenuated polio vaccine,

Tab. III. Obligatory since 2009 vaccination schedule published in 2011 by Polish Ministry of Health

Tab. III. Obowiązujący od 2009 r. kalendarz szczepień, opublikowany przez Ministra Zdrowia w 2011r.

Age period	Vaccine	Number of doses
1-year	HBV	3
	BCG	1
	Dt-Tt-P	3
	Hib	3
	I-PV	2
2-year	La-MMR	1
	Dt-Tt-P	1
	Hib	1
	I-PV	1
6-year	Dt-Tt-P	1
	I-PV	1
10-year	La-MMR	1
14-year	Dt-Tt	1

HBV - hepatitis B virus, BCG – tuberculosis, Dt – diphtheria toxoid, Tt – tetanus toxoid, P – pertussis, Hib - *Heamophilus influenza* type b , I-PV - inactivated polio vaccine, La-MMR - live-attenuated measles-mumps-rubella vaccine



BCG – tuberculosis vaccine, HBV – hepatitis B vaccines, Dt – diphtheria toxoid, Tt – tetanus toxoid, P - pertussis vaccine, PV – poliovirus vaccine, Ma – measles vaccine, Mu – mumps vaccine, R - rubella vaccine, Vv – varicella vaccine, Hibc – *haemophilus influenzae* type b conjugate vaccine, Pn – pneumococcal vaccine, InfV – influenza vaccine, Mn – meningococcal vaccine

Fig. 1. Vaccination rate before HSCT in autologous (A) and allogeneic (B) group

Ryc.1. Odsetek dzieci zaszczepionych przed autologicznym (A) i allogenicznym (B) przeszczepin komórek krwiotwórczych HSCT

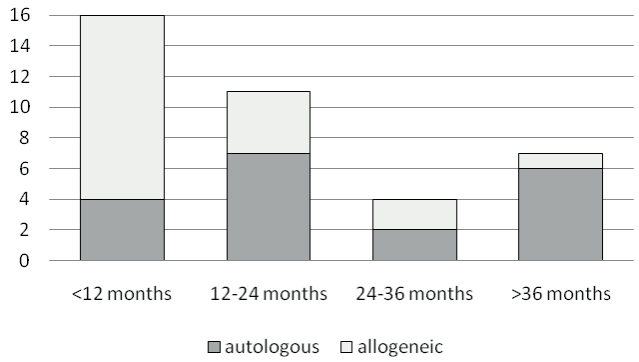


Fig. 2. The interval between HSCT and start of revaccination
Ryc. 2. Przedziały czasu między przeszczepieniem komórek hematopoetycznych i rozpoczęciem szczepień

First symptoms of primary disease were observed in the average of age 7.0 years (range: 0.2 – 17.5). Thus most of patients should complete main part of vaccination schedule before diagnosis of severe disease. The medical history reviled that only a few patients completed standard vaccination protocol before HSCT (fig. 1). Less than the half of children completed only a part of this program. Moreover, many of patients had not been vaccinated at all. The results for each vaccine were similar in autologous and allogeneic HSCT group (p=NS) and indicate that majority of children treated with HSCT couldn't have protective concentration of antibodies for vaccine-preventable diseases even primary.

The concentration of antibody for HBV, D, T, Hib and V was measured at the time of start revaccination. The interval between HSCT and revaccination was <12 months in 16 patients (12 allogeneic and 4 autologous); 12 - 24 months in 11 patients (4 allogeneic and 7 autologous); 24 – 36 months in 4 patients (2 allogeneic and 2 autologous) and >36 months in 4 patients (1 allogeneic and 3 autologous; fig 2). The mean concentration of antibody for HBV, D, T, Hib and V detected at the median time of 29 (range 6 – 67) months after autologous and 13 (range 8 – 33) months after allogeneic HSCT, before revaccination was commenced, is shown in fig. 3.

Before revaccination protective antibody levels were found for HBV in 54% of patients (geometric mean concentration /GMC/ 69 IU/ml, protective concentration /PC/ >10 IU/ml), for D in 62% (GMC 0.29 IU/ml, PC 0.10 IU/ml), for T in 18% (GMC 0.35 UI/ml, PC 0.10 UI/ml), for Hib in 29% (GMC 1.40 UI/ml, PC 0.10 UI/ml) and for V in 27% (GMC 7.20 UI/ml, PC 5.00 UI/ml). The rate of protection against analyzed pathogens in autologous and allogeneic group was similar and is shown in fig. 4.

DISCUSSION

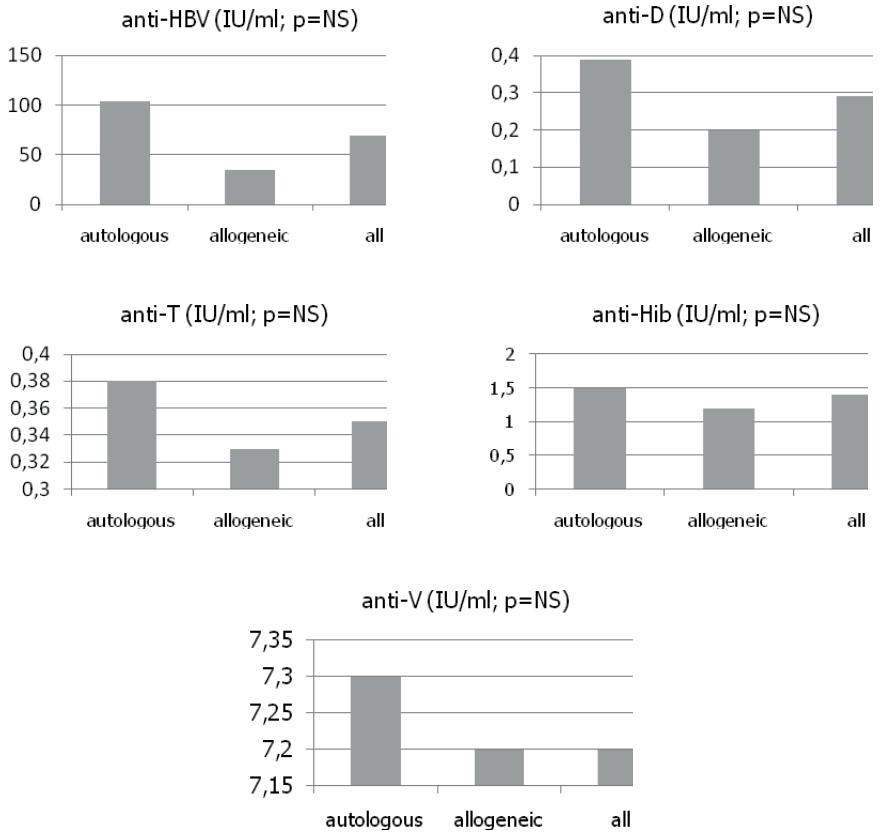
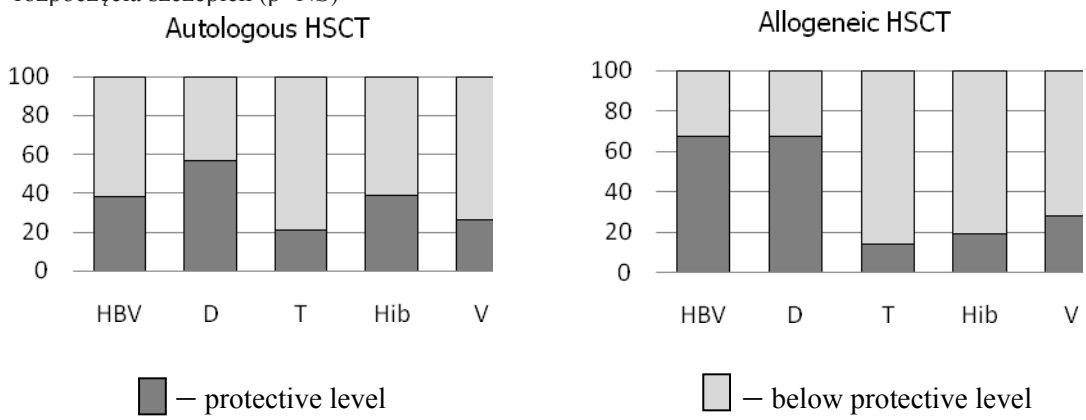


Fig. 3. The geometric mean concentration of antibody detected at the time of revaccination was commenced
Ryc.3. Średnie geometryczne stężenie przeciwciał mierzone w czasie rozpoczęcia szczepień

Fig. 4. The rate of protection against vaccine-preventable disease in autologous and allogeneic group at the time of revaccination was commenced (p=NS)

Ryc.4. Odsetek osób po przeszczepieniu autologicznym i allogenicznym z ochronnym poziomem przeciwciał w czasie rozpoczęcia szczepień (p=NS)



D – diphtheria, HBV – hepatitis B virus, Hib – *Haemophilus influenzae* type B, T – tetanus, V – varicella

Immunization, which is not for various reasons introduced consistently at all transplant centers (12), are important for two main reasons. First, the most important, is the need to protect the patients treated with HSCT against serious vaccine-preventable infections that may occur after transplant (7). Second, is the public health consideration point of view, to lower number of individuals vulnerable to important infections agents (6). Moreover, no data are currently available to suggest that routine immunization after HSCT should not be recommend.

During the last three decades, several studies have been published regarding the loss of pretransplant immunity. The most important factors are: type of transplant (autologous or allogeneic), regimen given before transplant, appearance and intensity of GvHD, immunosuppressive therapy given afterwards, type of donors and their serological status. The loss of immunity seems to depend on the strength of existing pretransplant immunity in the patients and, to some extent, the immunity status of the donor (6).

Especially in children after HSCT it should be expected more rapid loss of immunity or total lack thereof, due to the primary serious disease.

In our study the scheduled vaccination protocol was performed only partially, or patients were not vaccinated at all even though children were diagnosed with a mean of 7 years (fig.1). Despite same differences in recovery of immunity after autologous and allogeneic HSCT, the risk of losing immunity to several infections agents (e.g. hepatitis B virus, tetanus, diphtheria, varicella and *Haemophilus influenza* type b) are similar in both groups.

Although exists the hypothesis that immunity can be transferred adoptively from the donor to the recipient through an allograft, the durability of this immune response is uncertain, and most data suggested a fall in the antibody titers during the 1 – 10 years after HSCT, if the recipient is not revaccinated. Moreover, adoptive transfer of antibody responses is possible only for recall antigens. Transfer of responses to priming antigens, which would broaden the range of organisms against which patients can be protected is not successful (13).

Some of authors suggested that the transfer of immunity may be a consequence of mature T and B cells contamination of the harvested donor marrow or blood stem cell (13). Virtually all HSCT recipients rapidly loss all T- and B-lymphocytes after conditioning regimen (high dose chemotherapy with or without radiation or immunosuppressive therapy), losing immune memory accumulated through a lifetime of exposure to infections agents, environmental antigens, and vaccines. Most of the circulating T cells in the first year after transplantation, particularly in adults, are memory/effector T cells, likely derived from cells infused with the graft and capable of responding to antigens encountered by the donor before transplant. Naïve T cell capable of responding to new antigens are generated > 6 - 12 months after HSCT. Similarly, regardless of the time to recovery, newly generated B cells often show impaired antigen specific responses because of limited capability of naïve B cells to undergo somatic mutation and isotype switching during the first year after HSCT (7).

In presented group at the median time of 29 (range 6 – 67) months after autologous and 13 (range 8 – 33) months after allogeneic HSCT, when the revaccination was commenced, the majority of children had concentration of antibody lower than the minimum protective thresholds for tetanus (82%), Hib (71%), varicella (71%), HBV (46)% and diphtheria (38%).

This results strongly suggest a routine revaccination in all HSCT pediatric recipients after transplantation so that they can experience immunity to the vaccine-preventable diseases as others in general population.

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Authors declare non conflict of interests.

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