UNIVERSIDADE ESTADUAL PAULISTA "JÚLIO DE MESQUITA FILHO"
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DIFICULDADES ENCONTRADAS NO PROGRAMA DE REVACINAÇÃO DOS PACIENTES SUBMETIDOS AO TRANSPLANTE DE CÉLULAS TRONCO HEMATOPOIÉTICAS

Dissertação apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Mestre em Biotecnologia Médica.

Orientadora: Profa. Dra. Clarisse Martins Machado

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DEDICATÓRIA

*Aos meus pais, **Sebastião e Bárbara**, pela dedicação, incentivo e pelo exemplo de vida. Sem vocês este trabalho e muitos dos meus sonhos não se realizariam.*

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EPÍGRAFE

"É necessário estar sempre à espera de que um novo conhecimento surja, superando outro que, já tendo sido novo, envelheceu."

Paulo Freire

ABSTRACT

Abstract

SILVA, P. M. **Difficulties of revaccination program in hematopoietic stem cell transplantation recipients**. 2016. Thesis (Master) – Faculty of Medicine of Botucatu, Universidade Estadual Paulista, Botucatu, 2016.

A revaccination program is recommended for all HSCT recipients. Despite the excellence of the Brazilian revaccination program, several pitfalls have been observed over the years. We evaluated such pitfalls and how a prospective and tailored follow-up may help to overcome these obstacles. HSCT recipients (n=122) were followed prospectively and categorized into Group 1 (n=72), recipients who had already started the revaccination program and Group 2 (n=50), recipients who were up to start the vaccines. Whenever a gap on the program was encountered or a difficulty was reported, interventions and subsequent evaluations were performed. Problems related to patient compliance were less frequent than those related to HSCT center modifications of previous recommendations, or to errors made by the vaccination center. Advisory intervention was needed in 64% and 46% of Group 1 and Group 2, respectively (p=0.05), and were partially successful in around 70% of the cases. Total resolution was achieved in more than 35% in both groups. Although the Brazilian revaccination program is excellent, it needs to be improved and all efforts should be made to guarantee a safe and complete revaccination schedule. HSCT centers should appoint nurses and transplant infectious disease physicians to organize and to monitor the progress of the program.

Keywords: hematopoietic stem cell transplantation, immunization, difficulties in revaccination.

RESUMO

Resumo

SILVA, P. M. **Dificuldades encontradas no programa de revacinação dos pacientes submetidos ao transplante de células tronco hematopoiéticas**. 2016. Dissertação (Mestrado) – Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu, 2016.

Um programa de revacinação é recomendado para todos os receptores de TCTH. Apesar da excelência do programa de revacinação brasileiro, várias dificuldades têm sido observadas ao longo dos anos. Avaliamos essas dificuldades, e como um follow-up prospectivo e adaptado poderia ajudar a superar esses obstáculos. Receptores de TCTH (n=122) foram acompanhados prospectivamente e categorizados em Grupo 1 (n=72), receptores que já haviam iniciado o programa de revacinação e Grupo 2 (n=50), receptores que iniciaram a vacinação após inclusão no estudo. Sempre que uma falha no programa foi encontrada ou uma dificuldade informada, intervenções e subsequentes avaliações foram realizadas. Problemas relacionados à adesão dos pacientes foram menos frequentes do que as relacionadas às modificações das recomendações anteriores do centro de TCTH, ou a erros cometidos pelo centro de vacinação. Intervenções foram necessárias em 64% e 46% nos Grupos 1 e 2, respectivamente (p=0,05), e foram parcialmente bem sucedidas em aproximadamente 70% dos casos. A total resolução foi alcançada em mais de 35% em ambos os grupos. Embora o programa de revacinação brasileiro seja excelente existe a necessidade de aperfeiçoa-lo, e todos os esforços deveriam ser feitos para garantir um programa de revacinação seguro e completo. Os Centros de TCTH deveriam indicar enfermeiros e infectologistas de transplante para organizar e monitorar o progresso do programa de revacinação.

Palavras-chave: transplante de células tronco hematopoiéticas, imunização, dificuldades na revacinação.

LISTA DE ABREVIATURAS

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ALL – acute lymphoid leukemia

AML – acute myeloid leukemia

CML - chronic myeloid leukemia

CPH – células progrenitoras hematopoiéticas

CRIE – Centro de Referência de Imunobiológicos Especiais

CTP – células tronco periféricas

DECH – doença do enxerto contra hospedeiro

G-CSF - Granulocyte colony-stimulating factor

GVHD - graft versus host disease

HAC - Hospital Amaral Carvalho de Jaú

HLA - antígenos leucocitários humanos

HSCT – hematopoietic stem cell transplantation

IDSA – Infectious Diseases Society of America

MM – multiple myeloma

MO – medula óssea

PBSC - Peripheral blood stem cell

TCTH – transplante de células tronco hematopoiéticas

TID – transplant infectious diseases

SUMÁRIO

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INTRODUÇÃO

1 INTRODUÇÃO

1.1 Transplante de células tronco hematopoiéticas

O transplante de células tronco hematopoiéticas (TCTH) tem sido amplamente utilizado no tratamento de doenças oncológicas e hematológicas. Consiste na infusão intravenosa de células tronco hematopoiéticas (CTH) com o objetivo de restabelecer a hematopoese após regimes de radioterapia e/ou quimioterapia imunossupressora (1–3).

As CTH residem em pequenos números na medula óssea dos mamíferos adultos, e são necessárias ao longo da vida para repor as células sanguíneas maduras das diversas linhagens hematopoiéticas. As células tronco são definidas como células indiferenciadas capazes de se dividirem por períodos indefinidos de auto renovação e de gerar descendência de células altamente especializadas (4).

O TCTH pode ser realizado de três diferentes formas, através do transplante singênico, alogênico e autólogo. O TCTH singênico consiste na infusão de CTH de um irmão gêmeo idêntico saudável. O TCTH alogênico consiste na infusão de CTH de um doador compatível aparentado ou não. Esta modalidade de transplante é indicada no tratamento de doenças como leucemias, linfomas, mielodisplasias, síndrome de falência medular, imunodeficiências congênitas, deficiências enzimáticas e hemoglobinopatias. A compatibilidade entre doador e receptor é definida pelo estudo dos antígenos leucocitários humanos (HLA). O TCTH autólogo é realizado com as CTH do próprio paciente, indicada no tratamento de doenças neoplásicas e autoimunes. A indicação do tipo de transplante depende da doença de base, buscando sempre a infusão de CTH em qualidade e quantidades adequadas e sem contaminação com células malignas (1,5,6).

Existem, atualmente, três opções de fontes de CTH para transplante, medula óssea (MO), células tronco do sangue periférico (CTP) mobilizadas, e sangue do cordão umbilical. Há 30 anos, aproximadamente, utilizava-se apenas a MO como fonte de CTH, coletada da crista ilíaca posterior do doador, sob anestesia geral. Com a constatação da presença de CTH no sangue periférico, investigou-se seu uso como alternativa para o fornecimento destas células, podendo ser utilizadas tanto

em transplantes autólogos quanto alogênicos. A mobilização das CTP pode ser alcançada através do uso de fatores de crescimento, como G-CSF, e/ou quimioterapia. O uso desta estratégia aumenta o número de CTH circulante em 100 vezes ou mais. Outra opção são as células do sangue do cordão umbilical não manipulada e criopreservada ao nascimento (7,8).

O sistema imune do receptor deve sofrer uma ablação praticamente total, com o objetivo de prepará-lo para receber as CTH e não estabelecer uma resposta de rejeição. Este processo é denominado regime de condicionamento pré-transplante. Os pacientes são submetidos a doses elevadas e potencialmente curativas de drogas quimioterápicas, associadas ou não à radioterapia, tendo como resultado uma intensa depleção de todas as células hematopoiéticas do sistema imunológico, particularmente os linfócitos (3,9).

O principal objetivo do regime de condicionamento é o controle da doença a longo prazo. A necessidade de imunossupressão aumenta com o aumento da disparidade nos principais antígenos de histocompatibilidade. Os desejáveis resultados alcançados através do condicionamento são acompanhados por complicações relacionadas à alta toxicidade deste tratamento, como toxicidade cardíaca, toxicidade pulmonar, mucosite, toxicidade hepática, toxicidade da bexiga, toxicidade renal e toxicidade neurológica. A completa enxertia do receptor de TCTH acontece quando o sistema linfohematopoiético do paciente é totalmente substituído pelo enxerto recebido (6,10).

1.2 Perda da imunidade

Após o transplante, ocorre um estado temporário de imunodeficiência combinada em todos os pacientes, com recuperação funcional progressiva da imunidade humoral e celular durante os primeiros meses após o transplante. No acompanhamento a longo prazo após o TCTH, infecções graves, recaídas ou neoplasias podem estar diretamente relacionadas a persistência da deficiência imunológica. Diversos componentes dos mecanismos de defesa são prejudicados, incluindo barreiras mucosas, granulócitos, células *natural killer*, células-T e células-B. A memória imunológica acumulada durante toda a vida através da exposição à

agentes infecciosos e vacinação será perdida. Embora dados da literatura apontem para a transferência da memória de células-B do doador para o receptor, a maioria das células-B dos receptores provavelmente se desenvolvem à partir das CPH, que necessitam ser estimuladas para fornecer proteção a longo prazo (11,12).

A perda da memória imunológica parece depender da força imune que os pacientes apresentam antes do TCTH, e do estado imunitário do doador. Por exemplo, pacientes que foram vacinados contra sarampo são mais suscetíveis a perder a imunidade do que aqueles que experimentaram a infecção natural pelo patógeno. O estado de imunodeficiência coloca o receptor de TCTH em risco aumentado para infecções provocadas por uma variedade de patógenos, alguns dos quais podem ser prevenidos através da vacinação. Se o paciente não for revacinado após o TCTH, os títulos de anticorpos para doenças imunopreveníveis (por exemplo, sarampo, caxumba, rubéola, tétano, poliomielite) irão diminuir durante um período de um à dez anos após o TCTH. Portanto, um programa de revacinação é recomendado após o TCTH, tanto para receptores de TCTH alogênicos como autólogos (11,13,14).

1.3 Reconstituição imunológica

A reconstituição imunológica é essencial para o sucesso do transplante, uma vez que desempenha importante papel na defesa contra agentes patogênicos. Em geral, esse processo assemelha-se ao do desenvolvimento imune no inicio da vida embrionária. O elevado grau de morbidade e mortalidade dos pacientes pós-transplante estão relacionados ao atraso da recuperação do sistema imune. Após o TCTH dois fenômenos distintos ocorrem, a recuperação do número de elementos celulares da medula óssea e a recuperação funcional das interações celulares, sendo elas a recuperação natural (inata) do sistema imune, geralmente nos primeiros meses, e a adaptativa, que ocorre de forma gradual, e se estende pelos dois primeiros anos pós transplante (3,9).

Em geral, inicialmente ocorre o surgimento de células-T $CD4^+CD45RO^+$ nos primeiros dias pós TCTH; a inversão da razão $CD4^+$:$CD8^+$ nos dias seguintes; e a rápida normalização da contagem de células Natural Killer ($CD16^+CD56^+$). A

imunidade adaptativa se desenvolve ao longo do período pós transplante em decorrência da exposição a diversos antígenos ou à imunização ativa que se faz necessária nestes pacientes. A recuperação da imunidade humoral é mais lenta, o retorno da produção de anticorpos classe IgM para níveis normais ocorre gradualmente, sendo que a produção de IgG e de IgA persiste em quantidade insuficiente por mais de um ano (3).

O processo de reconstituição imune pode ser afetado por muitas variáveis, como o regime de condicionamento, a fonte de CTH, a ocorrência da DECH e o efeito de sua terapia, a presença de linfócitos maduros do doador e principalmente a função tímica do receptor. Os neutrófilos presentes no doador possuem pequeno impacto nas células circulantes no receptor, já os linfócitos maduros presentes no enxerto podem contribuir funcionalmente para a imunidade do receptor no período pós-TCTH. Frente ao complexo processo do transplante é impossível quantificar o impacto individual destes fatores sobre o enxerto, uma vez que todos podem interferir na reconstituição imune (3,9,15).

1.4 Programa de revacinação pós TCTH

A revacinação é indicada a todos os receptores de TCTH no período pós-transplante, uma vez que ocorre a perda da memória imunológica acumulada durante a vida. Inicialmente foram propostos diferentes calendários de vacinação para pacientes submetidos ao TCTH autólogo ou alogênico, no entanto, evidências sugerem que as perdas imunes são semelhantes, uma vez que estes pacientes receberam múltiplas doses de quimioterapia antes do transplante. Desde 1995, vários grupos têm trabalhado no aprimoramento e padronização dos protocolos de revacinação pós-transplante (14,16).

Na elaboração de um programa de revacinação para o receptor de TCTH alguns pontos devem ser levados em consideração. Em primeiro lugar, a escolha das vacinas deve ocorrer a partir da avaliação do risco e gravidade das infecções contra as quais estas vacinas são direcionadas, podendo ser subdivididas em: a) infecções mais frequentes e graves nos receptores de TCTH do que na população em geral, como aquelas provocadas pelo *Streptococcus pneumonia* (pneumococo),

Haemophilus influenzae tipo B (Hib), varicela-zoster, e o vírus influenza; b) infecções que não são mais frequentes nos pacientes transplantados do que na população em geral, como tétano, difteria, pólio, e hepatite B, mas que devem ser garantidas ao receptor de TCTH por uma questão de saúde publica; c) infecções a serem consideradas em situações especiais, como para pacientes residindo em certas regiões endêmicas ou para viajantes. Em segundo lugar, deve ser levado em conta o risco de eventos adversos. Vacinas contendo organismos vivos apresentam potencial para provocar infecções graves e disseminadas nos imunossuprimidos, neste caso, as vacinas contendo organismos vivos não devem ser utilizadas, ou apenas em circunstâncias previamente definidas (13).

O Brasil possui um Programa Nacional de Imunização (PNI), ativo e gratuito, para toda a população brasileira, que tem como missão o controle, a erradicação e a eliminação de doenças preveníveis. As ações de vacinação são compartilhadas pela União, pelos estados, pelo Distrito Federal e pelos municípios. A imunização de pacientes imunocomprometidos e a distribuição dos imunobiológicos especiais, é gerenciada pelos Centros de Referência de Imunobiológicos Especiais (CRIEs), distribuídos regionalmente em todo o país. A Unidade Básica de Saúde é responsável pelo atendimento na atenção básica e integral da população, de forma programada ou não (17-19).

De acordo com a última versão do Manual do CRIE as vacinas recomendadas para os pacientes pós TCTH são: vacina adsorvida difteria, tétano e pertussis (DTP), vacina adsorvida difteria, tétano e pertussis acelular (DTPa) ou vacina adsorvida difteria e tétano adulto (dT), vacina *Haemophilus influenzae* b (Hib), vacina inativada contra poliomielite 1, 2, 3 injetável (VIP), vacina contra hepatite B (HB), vacina contra hepatite A (HA), vacina contra sarampo, caxumba e rubéola (SCR), vacina pneumocócica 10-valente conjugada (Pn10), vacina pneumocócica 23-valente de polissacarídeos (Pn23), vacina contra varicela (VZ), vacina inativada contra *influenza* (INF), vacina contra febre amarela (FA) e vacina conjugada meningocócica C (MncC) (18,20).

O Serviço de Transplante de Medula Óssea do Hospital Amaral Carvalho de Jahu (HAC/Jaú) e o Grupo Cooperativo do Hemocentro da Universidade Estadual Paulista de Botucatu iniciaram suas atividades em agosto de 1996, sendo que até novembro de 2015 foram realizados 2.496 TCTH. Este serviço tem se firmado ao longo destes anos, tornando-se um dos maiores centros de referência nacional. No

HAC/Jaú existe uma proposta de esquema vacinal sendo utilizada, baseada no atual Manual CRIE e no IDSA Guideline.

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PAPER

2 PAPER

DIFFICULTIES OF REVACCINATION PROGRAM IN HEMATOPOIETIC STEM CELL TRANSPLANTATION RECIPIENTS

2.1 Introduction

After hematopoietic stem cell transplantation (HSCT), a temporary state of combined immunodeficiency occurs, with gradual recovery of humoral and cellular immunity during the early years of transplantation (1). The immunodeficiency state places the recipient at an increased risk for a variety of pathogens, some of which may be prevented by immunization (2–4).

Antibody titers to vaccine-preventable diseases, such as tetanus, diphtheria, polio, or measles, decrease during one to ten years after the HSCT (6–9). Therefore, a revaccination program is recommended for both allogeneic and autologous HSCT recipients (2,5,10,11).

The difference between the ideal scenario presented in guidelines and real-life scenarios is one of the most recognized barriers to the implementation of recommended practices (12). The Brazil has a national immunization program, which guarantees full and free access for all population. Through the National Immunization Program, the Brazilian Ministry of Health offers a free vaccination program for immunocompromised patients managed by Reference Centers for Special Immunobiologicals (CRIE), spread regionally across the country. Despite the excellence of the revaccination program, several pitfalls have been observed over the years.

2.2 Objectives

The present study aimed to demonstrate the pitfalls encountered in the post

HSCT revaccination process, and how a prospective and tailored follow-up developed by a specialized nurse and a transplant infectious disease physician may help to overcome the obstacles.

2.3 Methods

The study was conducted at the outpatient setting of the HSCT Program of Amaral Carvalho Foundation (ACF), in the city of Jahu (SP, Brazil) from January to December 2014.

Population. Patients from all states of Brazil are referred to our center to undergo HSCT. 130 patients, non-randomly and not controlled, were included in the study during the medical appointments at the outpatient setting. Three patients were excluded because of death or relapse of the disease before starting the revaccination protocol and five patients signed the informed consent but did not comply with the follow-up. Thus, 122 HSCT recipients were analyzed.

Revaccination Program. The revaccination program begins around the fourth month of transplantation, and in general, all patients return to their hometowns to start vaccines locally. Table 1 shows the revaccination calendar proposed by the Amaral Carvalho Foundation HSCT center, in comparison to the CRIE's (13) and the IDSA Guidelines' calendar (14).

Table 1 - Proposed number of vaccine doses in different HSCT revaccination calendars

Vaccines	CRIE 2014	IDSA Guidelines 2013	HAC – Jahu
Pneumococcal conjugate (PCV-10 or PCV-13)	3 (≤5 years only)	3	3
Pneumococcal polysaccharide vaccine(PPV-23)	2	1	1
Tetanus, diphtheria (Td)	3	3	3
Tetanus, diphtheria, acelular pertussis (DTPa) (<7 yr)	3	3	3
Haemophilus influenza conjugate (Hib)	3	3	3
Meningococcal conjugate (MCV)	1	2	2
Inactivated polio (IPV)	3	3	3
Recombinant hepatitis B (HBV)	3	3	3
Hepatitis A vaccine (HAV)	2	Follow recommendation for general population	2
Human papillomavirus (HPV)	0	3 (female aged 11-26 yr years and HPV4 vaccine for males aged 11-26 yr)	0
Inactivated influenza (INF)*	1-2 (annually)	1-2 (annually)	1-2 (annually)
Measles-Mumps-Rubella (MMR)**	2	2	1
Varicella (Varivax)**	2	2	0
Yellow fever (YFV)**	1	Follow recommendation for general population	0

*Two doses if < 9 years of age; **Live vaccines, only recommended after the 2nd year and without immunosuppression

Study design. Quantitative, non-randomized and single-center study, including two cohorts of patients: Group 1) patients who had already initiated the revaccination process; Group 2) patients who were close to start the program. Group 1 consisted of 72 HSCT recipients (59%), at a median of 363 days after HSCT (range 106-722) who

had already started the revaccination program. After signing the informed consent, patients were questioned about the difficulties related to the revaccination program. Following, their vaccination cards were compared to the local protocol and designated as appropriate or not, according to the time after vaccination start. After this initial retrospective evaluation, patients from Group 1 were prospectively followed up to the end of their revaccination process. Group 2 consisted of 50 HSCT recipients (41%) at a median of 138 days after HSCT (range 94-462) who were close to start the revaccination program. After a brief explanation, patients were referred to the vaccination centers. Patients after the second year of HSCT were not included in the study; therefore, delays or problems regarding live virus vaccines were not analyzed.

Definitions. According to our vaccination program, patients are expected to complete the vaccine calendar after 8 months after starting revaccination, except by the live virus vaccines. Those who did not complete the expected schedule were considered out of step. The main reasons for the failures were categorized into the following categories: 1) related to patient compliance; 2) related to HSCT center modifications of previous recommendations; and 3) related to errors of public vaccination centers.

Follow-up. All information provided by the patients was recorded in a data collection form (appendix A). Copies of the vaccine cards were taken at inclusion and regularly thereafter to track the progress of revaccination. Patients were followed prospectively by phone calls, emails, mobile applications on cell phones, or personally during the medical appointments. Whenever a gap on the vaccination program was encountered or a difficulty was reported, personalized interventions and subsequent evaluations were performed. Interventions always focused the needs of each patient, and a close contact with the vaccination centers were maintained through phone calls and orientation letters.

Ethical issues. The study was analyzed by the Ethics Committee of the Amaral Carvalho Foundation and is available at http://aplicacao.saude.gov.br/ plataformabrasil/login.jsf. The patients were informed about the risk and benefits of the research and signed the “Informed consent”, according to the 466/12 resolution of the National Health Council.

Statistical analysis. Continuous variables were expressed as medians. Comparison of qualitative or categorical variables were analyzed using the chi-

square test. Logistic regression analysis was performed to determine the variables associated with delays in the revaccination program (software SPSS version 19.0).

2.4 Results

The characteristics of the patients analyzed in the study are shown in table 2.

Table 2 - Characteristics of HSCT recipients (N=122)

	Group 1	**Group 2**	***p*-value**
No of patients (%)	72 (59)	50 (41)	
Median age	36 (3 – 72)	27 (1 – 66)	0.15
Sex			
Female	26 (36.1)	22 (44)	0.38
Male	46 (63.9)	28 (56)	
Region			
Midwest	2 (2.8)	3 (6)	0.18
Northeast	18 (25)	13 (26)	
North	2 (2.8)	6 (12)	
Southeast	43 (59.7)	26 (52)	
South	7 (9.7)	2 (4)	
Underlying disease			
ALL	18 (25)	13 (26)	0.39
AML	19 (26)	10 (20)	
CML	10 (14)	2 (4)	
MM	5 (7)	10 (20)	
Other	20 (28)	15 (30)	
HSCT type			
Allogeneic RD/UD	52/11 (72/15)	24/12 (48/24)	0.04
Autologous	9 (13)	14 (28)	
Conditioning regimen			
Myeloablative/Non-M	50/18 (75/25)	45/5 (90/10)	0.03

Continuation of Table 2			
ATG use			
Yes/No	6/66 (8.3/91.7)	38/12 (24/76)	0.01
Stem cell source			
Bone marrow	38 (52.8)	24 (48)	0.39
Cord blood	2 (2.8)	0 (0)	
PBSC	32 (44.4)	26 (52)	

(RD=related donor; UD=unrelated donor; M=myeloablative)

The beginning of the vaccination program occurred at a median of 163 days (ranging from 69 to 489 days) in group 1 and 166 days (114 to 466) in group 2 (p=0.35).

Eleven from 72 patients (15.3%) in Group 1 and 11 from 50 in Group 2 (22%) presented pitfalls related to patient compliance (p=0.34). Forty one patients in Group 1 (56.9%), and 24 in Group 2 (48%) presented pitfalls related to HSCT center modifications of previous recommendations (p=0.33); and 41 (56.9%) and 25 (50%) patients in Groups 1 and 2, respectively, had pitfalls due to errors made by the vaccination center (p=0.44). In total, 105 HSCT recipients (86%) presented at least one problem, 63 (87.5%) in Group 1 and 42 (84%) in Group 2 (p=0.58) (table 3).

Table 3 - Problems in the revaccination program according to category and patient group (N=105).

Category	Problems	Group 1 (N=63) N (%)	Group 2 (N=42) N (%)	p-value
Patient compliance	Lack of commitment	6 (9.5)	2 (4.8)	0.36
	Difficulty to contact	6 (9.5)	4 (9.8)	0.94
	Misunderstanding of the recommendation	2 (3.2)	5 (11.9)	0.07
HSCT center	Delay without justification	6 (9.5)	3 (7.1)	0.66
	Delay due to complications	8 (12.7)	7 (16.7)	0.56
	Delay due to GVHD	21 (33.3)	5 (11.9)	**0.01**
	Delay due to immunosuppression w/o GVHD	7 (18.9)	6 (33.3)	0.23
Vaccination center	Lack of trained team/poor organization*	28 (44.4)	18 (42.9)	0.87
	Vaccine was not authorized	10 (15.9)	3 (7.1)	0.18
	Patients' perception of lack of commitment from the health professional	11 (17.5)	10 (23.8)	0.42
	Patients received a vaccine that was not indicated and could represent a risk for them	6 (9.5)	1 (2.4)	0.15

(*Various: use of vaccines that should not be applied; team unaware of the procedure to get specific vaccines; vaccine denied due to fear; vaccination denied because the patient "had already been vaccinated in childhood"; inadequate completion of the vaccination cards).

Delays in one or more vaccines were frequently observed (86/105, 81.9%). Table 4 presents the frequency of vaccine's delays.

Table 4 - Vaccine delays according to patient group (N=86).

Vaccine	Group 1 (N=57)		Group 2 (N=29)		p-value
	N	%	N	%	
Hib	29	50.9	21	72.4	0.05
MCV	32	56.1	3	10.3	<0.001
PCV10	31	54.4	9	31	0.04
HAV	18	31.6	2	6.9	0.01
PPV23	16	28.1	1	3.4	0.007
IPV	11	19.3	3	10.3	0.28
dT/DTP	10	17.5	3	10.3	0.37
HBV	6	10.5	3	10.3	0.97

Univariate analysis showed that type of transplant, myeloablative conditioning, GVHD, use of immunosuppressive drugs, clinical complications, adverse reactions and lack of patient compliance did not contribute significantly to vaccine delays. The non-authorization of vaccines by the vaccination center was the only variable that had a significant impact on the delay of the revaccination program, as shown in table 5.

Table 5 - Variables associated with vaccine delays (n=122).

Variable		Vaccine delay		p-value
		Yes (%)	No (%)	
Type of HSCT	Allo	72 (72.7)	27 (27.3)	0.26
	Auto	14 (60.9)	09 (39)	
Mieloablative conditioning	Yes	56 (74.7)	19 (25.3)	0.44
	No	16 (66.7)	08 (33.3)	
GVHD	Yes	24 (77.4)	07 (22.6)	0.32
	No	62 (68.1)	29 (31.9)	
Immunosuppression	Yes	11 (68.8)	05 (31.3)	0.87
	No	75 (70.8)	31 (29.2)	
Clinical intercurrences	Yes	13 (65)	07 (35)	0.55
	No	73 (71.6)	29 (28.4)	
Adverse reactions	Yes	05 (50)	05 (50)	0.13
	No	81 (72.3)	31 (27.7)	
Lack of patient compliance	Yes	08 (100)	0 (0)	0.06
	No	78 (68.4)	36 (31.6)	
Vaccine not authorized	Yes	13 (100)	0 (0)	0.01
	No	73 (67)	36 (33)	

Concerning to the pneumococcal conjugate vaccine, 19 patients in group 1 (26.4%) and 4 (8%) in group 2 (p=0.01), did not get the vaccine because the Brazilian Ministry of Healthy, following the recommendations in the vaccine package insert, does not allow its use in persons older than 5 years. In two patients, one in group 1 (1.4%) and one in group 2 (2%), the vaccination center considered that the PPV23 was enough and did not authorize the PCV (p=0.79). Only four (5.6%) and one (2%) patients in groups 1 and 2, respectively, were given a justification letter on

the non-realization of PCV vaccines by the vaccination center (p=0.33). The refusal of pneumococcal vaccine was not uniform, as some centers applied the vaccine without questioning.

Advisory intervention was necessary in 46 episodes in Group 1 (63.9%) and 23 in Group 2 (46%) (p=0.05). The results of the intervention did not differ significantly among groups, and were partially succesful in 30 (65,2%) of Group 1, with total resolution observed in 17 of them (37%). Similarly, partial success was achieved in 18 patients (78,3%) from Group 2, with total resolution of the problems in 9 of them (39%).

2.5 Discussion

Our study describes the pitfalls encountered by HSCT recipients who performed the revaccination calendar at their hometowns.

Current revaccination calendars include numerous vaccines, with different number and specific intervals between doses that should be managed to optimize the frequency of patient visits to the vaccination center, reflecting the complexity of the program. In addition, clinical complications may occur during patient follow-up and a trained team of health professionals is essential to evaluate the real need of vaccine postponing. Any rupture in this chain results in delay in the revaccination program.

Indeed, the main difficulty encountered in our study was vaccination delays (81.9%). In general, lack of patient compliance contribute less to revaccination pitfalls (around 20%) than the issues related to the HSCT unit or the vaccination centers (more than 50%).

Concerning to the HSCT center, a trained nurse may be an ideal supervisor for the revaccination program and, along with the transplant infectious diseases (TID) doctor, should organize the sector and promote the continued education of the HSCT team. Tracking of program progress can be made through vaccination cards, phone calls or text messages, facebook notes, etc, as suggested by some authors (15). Constant monitoring is the key to a successful revaccination program.

Our study showed that patients who were prospectively monitored by a trained nurse needed significantly less intervention (46%) than the group who had already

started their revaccination process (64%, p=0.05). Advisory intervention by the nurse and the TID doctor resulted in partial or total resolution of the problems, around 65% and 37%, respectively.

GVHD is a frequent reason reported by the HSCT team to postpone vaccines. In the 105 patients who had problems in their vaccination calendar, GVHD delayed vaccination in 24.7% of them. Group 1 accounted with the majority of the delays (33%) probably because those patients had already started the vaccine program before inclusion in the study. The advisory supervision by the nurse conducting the study significantly decreased the delays due to GVHD in Group 2, which was followed from the beginning of the protocol (table 3, p=0.01).

Postponing vaccination due to GVHD seems unjustified, as guidelines do not recommend with the exception of live vaccines (2,5,10). In addition, there is no evidence of exacerbation of chronic GVHD after the use of inactivated vaccines (16). Nevertheless, a survey conducted by HUDSPETH et al (2010)(5) demonstrated that most of the surveyed centers (59%) delayed not only live virus vaccines, but also inactivated vaccines in the presence of GVHD**.** Another study evaluating the vaccination practices for patients with GVHD showed that 30% of the transplant centers delayed all vaccines, 30% delayed only the live vaccines and 39% delayed all vaccines except by influenza and/or pneumococcal vaccine (12).

It is known that GVHD and its treatment may decrease vaccine responses to T-cell and antibodies (2,3,10,17,18) and that is the main excuse used by the HSCT team to postpone vaccination. A more recent communication from the International Consensus Conference on Clinical Practice in chronic GVHD proposed the postponement of vaccinations for up to 3 months in adult patients, if they are receiving three or more immunosuppressive agents for the treatment of GVHD (19). However, some of these patients may respond to vaccines. As the recommended vaccines (excepted by the live ones) are safe in the scenario of GVHD, some authors recommend to measure specific antibody levels before and after vaccination to evaluate protection and the need for booster doses (2,5).

Some authors have found that allogeneic HSCT recipients have frequent delays in the revaccination program due to recurrent clinical complications during follow-up (12). In our study, type of HSCT was not associated with vaccine delays. Allogeneic HSCT recipients presented similar rates of vaccine delay (72%), in comparison to autologous (61%, p=0.26). Other authors observed that patients undergoing

autologous or allogeneic transplants presented different problems causing missed and/or delayed vaccination, although no statistical comparison was made between groups (15).

A variety of immunization protocols has been proposed. In 1995, a survey developed among HSCT centers demonstrated that vaccines were improperly used, protocols were very different between centers and just few centers used multiple vaccine doses (5). Thus, it is clear that the acceptance of the recommended revaccination program varies between centers and, in some of them, up to 48% of the patients have no appropriate reason to be out of step with their vaccination calendar (15). Fortunately, our vaccination protocol seems to be accepted by the HSCT team. Only a small number of patients in both groups had vaccine delays without reason, 6 in group 1 (14.3%) and 5 in group 2 (18.5%, p=0.63).

Concerning to the vaccination centers, the most frequently problem encountered was the lack of a properly trained team and/or poor organization. Health personnel working at the Basic Health Units do not seek guidance from the CRIE, as how to obtain special immunobiologicals or how to manage adverse situations. The CRIEs should be the first to be consulted in these cases. In our study, more than 40% of the problems related to the vaccination center fell in this category. Moreover, 9.5% of the patients in group 1 and 2.4% in group 2 received live vaccines, incorrectly indicated considering the post-transplant period. Health professionals working in this scenario should have adequate training and frequent expert supervision to clarify doubts and reduce errors that can be life threatening.

Unfortunately, the cost effectiveness of the immunization program provided by the Brazilian Ministry of Health may result disappointing if properly trained health professionals were not available. Other authors analyzing the children's vaccine records and the health service at Botucatu city, SP, Brazil, observed that approximately 30% of the studied population were not informed about the applied vaccine, the next vaccines to be scheduled, the possibility of adverse reactions, or received inadequate information. The lack of orientation was the main cause of delayed vaccines, identified in 60% of the cases (20).

In our study, the highest proportion of delay was found with the MCV in patients from group 1 and with the Hib in patients from group 2. The vaccine against meningitis C has been recently incorporated to the CRIE's vaccination schedule as recommended to HSCT recipients, justifying the delay in 32 (56.1%) of the patients in

Group 1 (13). In previous international guidelines, meningococcal vaccine was just recommended if indicated (2,4). As patients in group 2 initiated the process using the updated protocol, only a few delays in MCV vaccine were observed in this group. The delay in carrying out the Hib vaccine in patients from group 2 was related to an interruption in the distribution of the vaccine by the National Laboratory, Bio-Manguinhos/Fiocruz, since November 2014 (21), while most of the patients in group 1 had already completed this stage of the protocol.

Although less frequent than the delays observed with MCV and Hib, the pneumococcal vaccines deserve especial comments. The first licensed conjugate pneumococcal vaccine was PCV7 (Prevnar, Pfizer, Inc. New York), which offers protection against serotypes 4, 6B, 9V, 14, 18C, 19F and 23F (22). This vaccine was proven to be immunogenic and safe in both child and adult HSCT recipients (23,24). The 10-valent pneumococcal vaccine (Synflorix, GSK, Brendford, UK) was also licensed in Europe, and uses different carrier proteins compared to PCV7 and offers seroprotection against three additional serotypes (1, 5, and 7F). The PCV10 was never tested in transplant patients (25).

In 2010, the new 13-valent pneumococcal vaccine (Prevnar13, Pfizer, Inc. New York), was already approved and being tested in HSCT recipients. At that moment, the recommendation has been to use PCV13, if the 7-valent vaccine were no longer available (25). The study evaluating the PCV13 in HSCT recipients has been recently published and confirmed the safety and effectiveness of the vaccine (11).

In Brazil, the PCV10 was introduced in the national immunization program in 2010 for children younger than 5 years old (14), and then included in the vaccination calendar of immunocompromised patients, as a substitute for the PCV7. The PCV13 is not offered by the Brazil Ministry of Health, its acquisition is only possible through the purchasing in private medical clinics.

In our study, the delay observed in pneumococcal vaccination was due to vaccine refusal by the vaccination center. The Brazilian Ministry of Health considers the PCV10 in adults “out of label” as the product label indicates its use in children up to 5 years (27). Unfortunately, since the PCV7 is no longer available, and the PCV13 is currently not included in the national program, an immediate change in this scenario seems unlikely and adults can only receive the PPV23.

However, some studies have shown that the best response to pneumococcal vaccine is observed when conjugate vaccines are used before the polysaccharide

vaccine. Roux et al compared the immunogenicity and safety of PCV7 with PPV in adults immunized at study entry and receiving a second dose of PCV7 or PPV after one year. The authors demonstrated that the highest responses occurred in the group receiving 2 doses of the conjugate vaccine, and the lowest responses were observed in the PPV/PCV7 group (23).

Cordonnier et al used the PCV7 vaccine in HSCT recipients with a median age of 37 years old, (range 7 to 59). The response to PCV7 given 3 months after transplantation was not inferior to the late start at 9 months of HSCT (79% in early and 82% in late vaccination). They also studied the effects of PPV23 vaccination after PCV7 in HSCT recipients, and showed that among patients who did not have a response after three doses of PCV7, 41% responded to the PCV7 antigens after receiving a dose of PPV23. Therefore, PPV23 not only may confer protection to 16 extra serotypes, but also may boost the response to the PCV7 serotypes. Thus, the authors recommended the use of 3 doses of PCV7 at monthly intervals, starting 3 months after HSCT transplantation, followed by one dose of PPV23 (24).

Recently, the same authors using 4 doses of PCV13 (3 doses with one month interval and a 4ª dose after 6 months) in pediatric and adult allogeneic recipients, identified an increase in antibody levels after 3 doses across all PCV 13 serotypes, with a significant decline in the next six months but, a new increase after the 4th dose. The use of PPV23 one month after the fourth dose usually maintained the antibody levels stable, even though an increase in systemic and local adverse reactions may occur (11).

Finally, the number of doses may also play an important role in vaccination delays. In our study, the vaccine against influenza virus was the only vaccine with no delay. Besides being a single dose vaccine, our institution develops a solid annual program to control respiratory virus transmission, targeting patients, caregivers and health professionals, which includes influenza vaccine campaign, which may explain this result (28).

Nelson et al evaluated the proper fulfillment of some vaccines that requires multiple doses (varicella, hepatitis A, and hepatitis B vaccine). Completion rates of all doses were higher for hepatitis B vaccine (55%-65% in most age groups) within a year, whereas hepatitis A and varicella vaccine compliance was lower (40%-50% for most age groups). The authors observed that compliance with multiple doses was low, particularly among adolescents, young adults and low socioeconomic level

individuals (29).

2.6 Conclusions

The study demonstrated that no matter the problem identified, the result to the patient will always be the delay in the revaccination program. The refusal in administrating the vaccine by the vaccination center was identified as the major reason for delays.

The conjugate pneumococcal vaccine should be urgently made available to adult HSCT recipients since there is scientific evidence of its safety and effectiveness.

Vaccination guidelines have been developed and updated, however, the Brazilian revaccination program needs to be adjusted and the Basic Health Units needs to improve the relationship with the CRIE, because many HSCT recipients remains unvaccinated, are vaccinated late, or undergo an incomplete schedule of vaccination.

All efforts should be made to assure that HSCT recipients have access to a safe and complete revaccination program. Our study showed that tailored follow-up performed by nurses and TID doctors helped to overcome the difficulties faced in this process.

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ANNEX A
TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

I. Registro das explicações do pesquisador ao participante a respeito da pesquisa.

Prezado(a) Senhor(a):

Você está sendo convidado(a) para participar do Projeto de Pesquisa sob o título: Dificuldades encontradas no programa de revacinação dos pacientes submetidos ao Transplante de Células Tronco Hematopoiéticas. Neste estudo queremos avaliar os problemas que os pacientes encontram ao procurarem os postos de saúde em suas respectivas regiões, para receberem as vacinas. Vamos avaliar também as falhas encontradas nas carteiras de vacinação.

Para isso, será necessário responder uma entrevista e apresentar sua carteira de vacinação. Você também poderá receber ligações a cada 15 dias para a coleta de informações. Seus dados serão confidenciais e o conteúdo da pesquisa será utilizado apenas para a realização do estudo, podendo ser publicado em congressos e revistas científicas. É importante que você saiba que vamos fazer uma cópia da sua carteira de vacinação.

A sua participação será totalmente voluntária, podendo deixar o projeto a qualquer momento, não havendo prejuízo para seu tratamento. Após receber os esclarecimentos e as informações, no caso de aceitar fazer parte do estudo, assine ao final deste documento, que está em duas vias. A via original é sua e a outra é do pesquisador responsável. Em caso de dúvida **sobre a pesquisa**, você poderá entrar em contato com a pesquisadora responsável Paula Moreira da Silva nos telefones: (14) 3602 1256 ramal 1433/(14) 98166-3179, e-mail pauladc@gmail.com, ou a orientadora Dra. Clarisse Martins Machado, no telefone (11) 3066 7020. Na ausência delas, as enfermeira Ana Claudia Ferrari dos Santos, no telefone (14) 3602 1256 ramal 1433 e Élen Monteiro da Silva, telefone (14) 3602 1257 ramal 1536 podem fornecer as informações sobre o estudo. Em caso de dúvida **sobre a ética aplicada a pesquisa**, você poderá entrar em contato com o Comitê de Ética em Pesquisa (CEP) do Hospital Amaral Carvalho de Jahu no telefone: (14) 3602 1194.

III. Custo de participação

Você não precisará pagar por nenhuma cópia, xérox relacionados à pesquisa. Não haverá nenhum pagamento pela sua participação no estudo.

II. Consentimento de participação da pessoa como sujeito da pesquisa

Eu, _____,
RG _____, abaixo assinado, concordo em participar do estudo **sob o título:** Dificuldades encontradas no programa de revacinação dos pacientes submetidos ao Transplante de Células Tronco Hematopoiéticas, como sujeito. Fui devidamente informado(a) e esclarecido(a) pela Enfermeira Paula Moreira da Silva sobre a pesquisa, os procedimentos nela envolvidos, assim como os possíveis riscos e benefícios decorrentes de minha participação. Entendo que as informações serão confidenciais e que posso retirar meu consentimento a qualquer momento, sem qualquer penalidade. Declaro que concordo em oferecer todas as informações solicitadas pelo(a) pesquisador(a), que fui convidado para participar deste estudo, e o faço voluntariamente.

Jahu, _____ de _____ de 20_____

_____

Assinatura do sujeito ou responsável

_____

Assinatura do pesquisador

APPENDIX A

FICHA DE COLETA DE DADOS

____/____/____

Nome:_____D.N.:_____/_____/_____

Idade:_____Sexo:_____RGP:_____

Cidade:_____Estado:_____

Diagnóstico:_____ Data TCTH:_____/_____/_____ D+:_____

Tipo TCTH:_____

Início vacinação: _____/_____/_____ Término vacinação: _____/_____/_____

Dificuldade no acesso à vacina? ( ) SIM ( )NÃO

Qual(is) vacina(s)?_____Data:_____/_____/_____

Qual(is) dificuldade? _____

_____

_____

Qual(is) vacina(s)?_____Data:_____/_____/_____

Qual(is) dificuldade? _____

_____

_____

Qual(is) vacina(s)?_____Data:_____/_____/_____

Qual(is) dificuldade? _____

_____

_____

Qual(is) vacina(s)?_____Data:_____/_____/_____

Qual(is) dificuldade? _____

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Qual(is) vacina(s)?_____Data:_____/_____/_____

Qual(is) dificuldade? _____

_____

_____

Qual(is) vacina(s)?_____Data:_____/_____/_____

Qual(is) dificuldade? _____

_____