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ORIGINAL ARTICLE

Immunization Status in Childhood Cancer Survivors: A Hidden Risk Which Could be Prevented

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Background: A limited number of studies have examined the vaccine-specific antibody status of children with cancer. There are disagreements over the guidelines for postcancer immunization strategy.
Methods: Our study was an observational, cross-sectional retrospective review of data collected on children who were seen in the outpatient clinic at King Abdullah Medical City, Oncology Center, Jeddah, the Kingdom of Saudi Arabia. Our aim was to evaluate the seropositive status to vaccine-preventable diseases: measles, mumps, rubella, diphtheria, tetanus, polio, and *Haemophilus influenzae* type B (HIB) in childhood cancer survivors at our center in order to plan future vaccination for these children and establish a simple revaccination schedule.
Results: Forty-seven patients (21 boys and 26 girls) were included in the study. Age at the time of cancer diagnosis (mean ± standard deviation) was 5.68 ± 3.79 years and age at test sampling was 10.68 ± 3.79 years. Acute leukemia was the most common cancer (49% of patients), followed by lymphoma (28%), brain tumors (13%), and solid tumors (10%). Treatment intensities (according to the Treatment Intensity Rating Scale, version 3.0; ITR-3) were 2, 3, and 4 for 26 patients (55%), 20 patients (43%), and one patient (2.1%), respectively. We found that 93% of our patients were considered seronegative (unprotected) for at least one vaccine-preventable disease. The seronegative rates for measles, mumps, rubella, diphtheria, tetanus, polio, and HIB were 46.8%, 36.2%, 36.2%, 46.8%, 61.7%, 17.1%, and 42.6%, respectively. Criteria including age at diagnosis, age at sampling, type of malignancy, and treatment intensity were not significantly different between seropositive and seronegative patients.
Conclusion: Seronegative rates for vaccine-preventable diseases were very high in childhood cancer survivors, which represented a subpopulation of high-risk patients who could benefit from revaccination. We suggest a universal revaccination approach for all childhood cancer survivors,

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which is easily applicable and of low cost.

1. Introduction

Malignancy in children and its treatment cause partial immune deficiencies, leading to increases of morbidity and mortality.[1,2] Declining levels of granulocytes, lymphocytes, and natural killer cells are associated with an increasing risk of bacterial, fungal, and protozoan infections.[3–5] Most children with cancer are diagnosed before completing their general vaccination programs and they also may undergo chemotherapy of variable intensity. Some children may become susceptible to infection as antibody levels achieved with vaccinations decline or disappear during the course of their disease and/or chemotherapy treatment. The clinical implications of losing protection against vaccine-preventable diseases are serious. There is risk for potentially life-threatening infections, and this immunocompromised group may serve as a reservoir for the spread of pathogens. Unfortunately, compliance with revaccination of childhood cancer survivors is poor.[6]

The aim of this study was to evaluate the serological status of childhood cancer survivors after the end of chemotherapy treatment and to estimate seronegative rates of vaccine-preventable diseases including measles, mumps, rubella, diphtheria, tetanus, pertussis, poliomyelitis, and *Haemophilus influenza* B (HIB). We also aimed to evaluate any risk factors associated with loss of protective antibodies.

2. Materials and methods

2.1. Patient population

During the period between July 2014 and December 2015, the data were reviewed for cancer survivors who were on long-term follow-up at King Abdullah Medical City Oncology Center, Jeddah. Clinical data of each patient were reviewed from patient medical records. Data for the vaccinations received were obtained from parents or the patient's immunization card. The study was approved by the Institutional Review Board of King Abdullah Medical City.

2.2. Inclusion criteria

The study included children aged 1–18 years who had completed their cancer treatment at least 3 months prior to data collection, were in remission, and who had their antibody levels checked for measles, mumps, rubella, diphtheria, tetanus, polio, and HIB vaccines. Blood samples were taken during routine follow-up blood work. Only patients with complete data were included.

2.3. Exclusion criteria

Children who received immunization postcancer treatment or who were on active treatment for cancer and/or who received blood or blood products including intravenous immunoglobulin in the preceding 3–6 months. Other exclusion criteria included previously diagnosed immunodeficiency or low immunoglobulin-G (IgG) levels in relation to age.

Age at the time of sample collection and the time since treatment completion were recorded.

2.4. Antibody assay

Different methods were used according to vaccine-specific antibodies as follows: measles, mumps, and rubella antibodies IgG by multiplex Flow Immunoassay (Rochester Lab, NY, USA); diphtheria toxoid IgG and tetanus toxoid IgG antibodies by the Enzyme Immune Assay (Rochester Lab, Rochester, NY, USA); poliovirus 1, 2, 3 neutralizing antibodies by enzyme-linked immunosorbent assay (Focus Diagnostics, Inc, CA, USA); and HIB antibodies (IgG) by enzyme-linked immunosorbent assay (Rochester Lab, Rochester, NY, USA).[7]

The results were either seropositive or seronegative based on the laboratory test manufacturer's guidelines. Patients who had the following levels were considered to have a protective titer for specific related infection (seropositive/protected): measles IgG $>$ 13.5 AU/mL, mumps $>$ 9 AU/mL, rubella $>$ 10.0 IU/mL, diphtheria toxoid IgG antibodies $>$ 0.01 IU/mL, tetanus toxoid IgG antibodies $>$ 0.01 IU/mL, polio neutralizing antibody titer 1:8 up to $>$ 1:28, and HIB IgG antibodies $\geq$ 1.0 mg/L.

For analysis purposes, patients were divided into two groups: "seropositive" or "protected" patients with antibody titers equal to or above previously cutoff levels, and "seronegative" or "unprotected" for those with antibody titers below the previously mentioned cutoff levels.

Treatment intensity was determined for each patient using a published scale using the Intensity of Treatment Rating Scale, version 3.0 (ITR-3). ITR-3 is a scale which classifies treatments into four defined levels of intensity based on diagnosis, stage, and treatment data (surgery, chemotherapy, radiation, and transplant) from medical records (Level 1 indicates least intensive treatments, Level 2 moderately intensive treatments, Level 3 very intensive treatments, and Level 4 most intensive treatments).[8]

2.5. Statistical analysis

Data analysis was mainly descriptive. Numeric data were presented as mean $\pm$ standard deviation (SD), or as median

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and interquartile range 25^{th}–75^{th} percentiles (IQR) according to the type of distribution of each variable. Frequency and percentages for categorical variables were used. The Chi-square test was used to compare between different variables. A p value < 0.05 was considered statistically significant.

3. Results

Forty-seven patients (21 boys [44.7%] and 26 girls [55.3%]) were included. The age at the time of cancer diagnosis (mean ± SD) was 5.67 ± 3.60 years, and the median was 4.39 years (IQR: 2.74–8.93 years). Patients' characteristics are summarized in Table 1.

Age at the time of sample collection (mean ± SD) was 10.27 ± 3.40 years, and the median was 12.55 (IQR: 7.84–10.06) years. Time from end of treatment to sampling (mean ± SD) was 3.02 ± 2.64 years, and the median was 1.90 (IQR: 0.74–5.09 years; minimum: 0.64 years, maximum: 8.59 years).

All patients had a normal level of IgG in relation to age. Total IgG level (mean ± SD) was 1242.97 ± 276.01 mg/dL, and the median was 1250.00 mg/dL (IQR 1060.00–1455.00 mg/dL; minimum: 687.0 mg/dL, maximum: 1840.00 mg/dL).

Regarding vaccines received prior to the start of cancer treatment, 20 patients (42.6%) were fully vaccinated (received all compulsory vaccines), whereas 23 patients (49.4%) were incompletely vaccinated, and only four patients (8.5%) had not received any vaccine according to the National Saudi Vaccination Program.

Treatment intensities as per the ITR-3 were 2, 3, and 4 of 26 patients (55%), 20 patients (43%), and one patient (2.1%), respectively.

Acute leukemia was the most common cancer in 23 patients (48.9%), followed by lymphoma in 13 patients (27.7%). Brain tumor was diagnosed in six patients (12.8%) and solid tumor in only five patients (10.6%). Different seropositivities for different vaccines in different types of cancer are shown in Table 2.

Our analysis revealed that 93% of our patients were considered to be seronegative for at least one vaccine-preventable disease. The seronegative rates for measles, mumps, and rubella were 46.8%, 36.2%, and 36.2%, respectively. Seronegative rates for diphtheria, tetanus, polio, and HIB were 46.8%, 61.7%, 17.1%, and 42.6%, respectively. Different criteria including age of diagnosis, age of sampling, type of malignancy, treatment intensity, and time of sample collection from end of treatment were not significantly different between seropositive and seronegative patients (Table 3).

Table 1 Characteristics of the children included in the study.

Variable	No. (%)
Sex	
Male	21 (44.7)
Female	26 (55.3)
Age at diagnosis (y)	
Mean ± SD	5.67 ± 3.60
Median (IQR)	4.39 (2.74–8.93)
Age at sample collection (y)	
Mean ± SD	10.27 ± 3.40
Median y (IQR)	12.55 (7.84–10.06)
Duration from end of treatment to testing (y)	
Mean ± SD	3.02 ± 2.64
Median y (IQR)	1.90 (0.74–5.09)
(minimum to maximum)	(0.64–8.59)
Treatment intensity received	
I	0
II	26 (55.3)
III	20 (42.6)
IV	1 (2.1)
Malignancy types	
Leukemia	23 (48.9)
Lymphoma	13 (27.7)
Solid tumor	5 (10.6)
Brain tumor	6 (12.8)
Vaccinations received prior to treatment	
Fully	20 (42.6)
Incompletely vaccinated	23 (49.4)
No vaccine	4 (8.5)

IQR = inter quartile range; SD = standard deviation.

4. Discussion

The percentage of childhood cancer survivors whose antibodies fall below the protective level differs widely. There is no clear clue to determine who is going to lose antibodies against which common vaccine antigens.

In our study, ~93% of patients were considered seronegative (unprotected) for at least one vaccine-preventable disease.

Age of the patients on diagnosis or age on sampling did not significantly differ between seropositive and seronegative patients. Similar findings have been reported previously,[9] but other studies reported that the younger the patient age upon cancer diagnosis the more rapid the decrease in protective antibody levels.[10–13]

We found that different types of cancer had no significant influence on antibody levels to different vaccines. Similar findings have been reported in a number of studies.[2,11,12,14] However, one study demonstrated that protection rates depended on the underlying malignancy and chemotherapeutic regimen.[15]

In our study, treatment intensity did not show a significant difference on antibody levels, which was similar to that reported by Patel at al.[9] However, other studies found that the intensity of acute lymphoblastic leukemia treatment could influence immune responses.[16–18]

In our study, the seronegative rates for measles, mumps, and rubella were 46.8%, 36.2%, and 36.2%, respectively. Seronegative rates for diphtheria, tetanus, polio, and HIB were 46.8%, 61.7%, 17.1%, and 42.6%, respectively. Significant post-treatment decreases in measles and mumps, diphtheria, and tetanus antibodies were observed in 43%, 31%, 52%, and 44% of the children, respectively.[13] Zignol et al[12] suggested that chemotherapy might induce a loss of protective serum antibody titers for rubella, mumps, and measles in 18%, 21%, and 25% of patients, respectively. Bochennek et al[19] reported loss of humoral immunity

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Table 2 Seropositive rates to different vaccines grouped according to underlying type of malignancy.

Vaccine	Leukemia $N = 23$ n (%)	Lymphoma $N = 13$ n (%)	Solid tumors $N = 5$ n (%)	Brain tumor $N = 6$ n (%)	p*
Measles	11 (47.8)	9 (69.2)	2 (40.0)	3 (50.0)	0.836
Mumps	13 (56.5)	9 (69.2)	5 (100.0)	3 (50.0)	0.444
Rubella	12 (52.2)	10 (76.9)	4 (80.0)	2 (33.3)	0.575
Diphtheria	9 (39.1)	10 (76.9)	3 (60.0)	3 (50.0)	0.375
Tetanus	7 (30.4)	8 (61.5)	1 (20.0)	2 (33.3)	0.438
Polio	20 (87.0)	12 (92.3)	4 (80.0)	3 (50.0)	0.199
Haemophilus	12 (52.2)	8 (61.5)	3 (60.0)	4 (66.7)	0.857

* A p value < 0.05 was taken to be significant.

Table 3 Seropositive rates of different vaccines grouped according to age on diagnosis and treatment intensity.

Vaccine	Serologic results		Age at diagnosis (y)			Age at testing (y)			Treatment intensity			
	Seropositive (protected) n (%)	Seronegative (unprotected) n (%)	< 7 $N = 32$ n (%)	> 7 $N = 15$ n (%)	p*	< 10 $N = 23$ n (%)	> 10 $N = 24$ n (%)	p*	II $N = 26$ n (%)	III $N = 20$ n (%)	IV $N = 1$ n (%)	p*
Measles	25 (53.2)	22 (46.8)	17 (53.1)	8 (53.3)	0.85	13 (56.5)	12 (50.0)	0.81	16 (61.5)	9 (45.0)	0	0.15
Mumps	30 (63.8)	17 (36.2)	19 (59.4)	11 (73.3)	0.45	12 (52.2)	18 (75.0)	0.34	16 (61.5)	14 (70.0)	0	0.65
Rubella	30 (63.8)	17 (36.2)	21 (65.6)	9 (60.0)	0.40	15 (65.2)	15 (62.5)	1.00	18 (69.2)	12 (60.0)	0	0.54
Diphtheria	25 (53.2)	22 (46.8)	16 (50)	9 (60.0)	0.79	12 (52.2)	13 (54.2)	0.81	14 (53.8)	10 (50.0)	1 (100)	0.80
Tetanus	18 (38.3)	29 (61.7)	11 (34.4)	7 (46.7)	0.42	7 (30.4)	11 (45.8)	0.53	10 (38.5)	8 (40.0)	0	0.90
Polio	39 (82.9)	8 (17.1)	28 (87.5)	11 (73.3)	0.48	20 (86.9	19 (79.2)	0.81	23 (88.5)	15 (75.0)	1 (100)	0.70
HIB	27 (57.4)	20 (42.6)	17 (53.1)	10 (66.7)	0.75	13 (56.5)	14 (58.3)	0.81	14 (53.8)	12 (60.0)	1 (100)	0.86

* A p value < 0.05 was taken to be significant.
HIB = *Haemophilus influenzae* type B.

against measles, mumps, and rubella in 27%, 47%, and 19% of patients, respectively. However, Nilsson et al[11] reported persistence of protective levels of antibodies in a high percentage of children after chemotherapy against measles (in 60%) and rubella (in 72%). Patel et al[9] also reported that the majority of children in their study had levels of protective antibodies for tetanus (100%), HIB (87%), and measles (71%) antigens.

In our study, loss of protective antibodies against polio was detected in 17.1% of patients. Zingol et al[12] reported losses of protective serum antibody titers in only 8% of patients. Another study reported a higher percentage of decrease of polio antibodies below the protective level in 12—25% of the children studied.[13] However, Patel et al[9] found only 11% of patients with acute leukemia had protective titers to all poliovirus serotypes after the end of the treatment.

Differences between studies may be due to variations in the types of vaccines used, populations, or treatment protocols. Also, different antibody tests and protective cutoff levels might also be responsible. Although the reason for the loss of protective vaccination antibodies in blood is not fully understood, the loss of humoral immunity has been demonstrated and linked to chemotherapy-induced alterations of the immune system.[20–23] Our practice during the study was to revaccinate all childhood cancer survivors according to specific antibodies results of each patient. For those who had an unprotective antibody titer, we recommended revaccination at the nearby primary health facility. Guidelines for child revaccination after end of chemotherapy are few. The United States guidelines (Centers for Disease Control and Prevention, 1993)[24] recommend revaccination 3 months after completion of chemotherapy. The current UK guidelines (Royal College of Paediatrics and Child Health, 2002)[25] recommend revaccination at 6 months after completion of standard chemotherapy. However, there is still debate with regards to the cost of universal revaccination after the end of cancer treatment, compared with the cost of laboratory antibody testing and then selective specific revaccination (which may be more costly and time-consuming). Also, there are still no clear cutoff levels for protective antibody titers to be used for revaccination in childhood cancer survivors. We agree with the previous opinion that universal revaccination is likely to be the most easily applicable, low-cost approach and therefore the most useful in developing countries.[9]

4.1. Limitations of the study

We did not measure vaccine antibodies at time of cancer diagnosis or after revaccination due to the high cost of antibody testing and limited resources. Also, there was no control group due to difficulties in recruitment and debate regarding the use of different levels of vaccines in healthy children's antibodies to be compared with those levels of cancer survivors.

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5. Conclusion

Seronegative rates for vaccine-preventable diseases were very high in childhood cancer survivors, which represented a subpopulation of high-risk patients who could benefit from revaccination. We suggest a universal revaccination approach for all childhood cancer survivors, which is easily applicable and of low cost.

Conflicts of interest

None.

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