Assessment of Humoral Immune Recovery in Children with Hematological malignancies after Completion of Chemotherapy

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Abstract

Background:

Childhood cancer is relatively rare, the most common types include, leukemias, brain cancers, and lymphomas. Children with cancer usually suffered from immunosuppression due to either the disease itself or its treatment. In this study, we aimed to assess the humoral immunity after completion of the treatment plan in children with hematological malignancies.

Patients and methods:

Twenty-nine patients were evaluated in a prospective study conducted between **March 2018 and April 2020** at the Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University. The patients were assessed for the concentration of total serum IgM, IgG, and specific measles IgM and IgG within one month after completing treatment, at 3 and 6months post-treatment, respectively.

Results:

The mean age of the patients was 6.36 ± 4.09 years, and 55.2 % were males. Patients with acute lymphoblastic leukemia (ALL) constituted 58.6% of the studied patients. Most patients (62.1%) were stratified as intermediate risk. Compared to normal reference values of immunoglobulins, our patients had significantly low levels of total IgM and total IgG at finishing chemotherapy (P <0.001), while at three and six months only total IgG continued to be significantly low (P=<0.001). As regard specific measles immunoglobulins (Igs), measles IgM was borderline higher (P=0.059) while measles IgG showed higher values compared to reference values (P=<0.001) at finishing treatment, both specific measles immunoglobulins increased significantly to levels higher than normal reference values at three and six months after finishing(P=<0.001). Less intensive treatment and duration of treatment had significantly affected the level of specific measles IgG (P=0.012, P=<0.05 respectively).

Conclusions:

Patients with hematological malignancies are vulnerable to humoral immune suppression at the end of the treatment, which persists for up to six months after stopping treatment. A shorter duration of treatment was the main factor that affected the immune recovery of our patients.

Keywords: humoral immunity, pediatric hematological malignancy, immunoglobulin, measles, ALL, immunodeficiency.

Introduction:

Childhood cancer is relatively rare, the most common types include, leukemias, brain cancers, and lymphomas. Children and adolescents who are diagnosed with cancer approximate 400 000 all over the world each year [1]. Survival rate of patients with cancer has been improved due to the advanced treatment strategy for pediatric malignant diseases. In recent years, 5-year survival rates for children with cancer have risen to ~80% in most high-income countries and up to 45% in low- and middle-income countries. This reflects partly the use of conventional and aggressive chemotherapy through better risk stratification of patients [2].

However, these strategies may lead to suppression of immune response in these patients. Children with cancer usually suffered from immunosuppression due to either the disease itself or its treatment. Certain cancer treatments (either chemotherapy or radiotherapy) can temporarily weaken the immune system by decreasing the number of leukocytes produced by the bone marrow and may lead to various types of infection [3]. The process of immune reconstitution can be variable depending on the nature of the disease, type and dosing of chemotherapeutic agents, and the age of the patient [4].

In this study, we aimed at assessing the status of the humoral immune system after finishing chemotherapy in children with hematological

malignancies including the possible factors that may affect the immune status.

Patients and Methods:

This prospective cohort study was conducted on pediatric patients with hematological malignancies (more than 2 years old) who finished their treatment between March 2018 and April 2020 at Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University. The study was approved by the local ethical committee and informed consent was taken from child's parents before including the child in the study. Children who were in complete continuous remission, within one month of their treatment protocol, were included in the study. Children less than two years old at the time of diagnosis, those who did not complete the obligatory vaccinations till diagnosis of their disease, patients with primary immune deficiency, or patients who underwent hematopoietic stem cell transplantation were excluded.

Patients' files were reviewed for age, sex, vaccination history, diagnosis, risk stratification, and treatment received (there were 29 patients included in the study, 12 patients received high dose cytarabine, 23 patients received high dose methotrexate (of them 9 patients received both high dose cytarabine and high dose methotrexate) and 25 patients received prolonged steroid, 5 patients received radiotherapy).

Every patient was assessed at three time points (baseline, within one month after finishing treatment, at three and six months after finishing) and subjected to complete history, physical examination (with special attention to manifestations of infection and nutritional status), routine laboratory investigations (complete blood count with concern on the absolute neutrophilic count and absolute lymphocytic count to ensure the hematologic recovery) and assessment of humoral immune status which included; total and specific measles IgM and IgG immunoglobulins.

Detection:

The results of **total human IgM and IgG** were compared to normal reference values according to that of Kardar et al **(Kardar *et al.*, 2012),** we used: Human IgM ELISA Kitt, Elabscience, Houston, Texas, United States, and Human IgG ELISA Kit. Elabscience, Houston, Texas, United States. **Specific measles IgM:** reference value (upper cut-off: 0.0827, lower cut-off:0.04708) (serion ELISA classic measles virus IgM. Würzburg, Germany). **Specific measles IgG:** Reference value (positive cut-off >11U/ml, zona intermedia:9-11/Uml, negative cut-off:<9U/ ml) (measles virus IgG, Homburg, Germany).

Several risk factors were studied and analyzed statistically in relation to the immunological status include patient-related factors: age and sex, disease-related factors: diagnosis, risk stratification: intermediate risk vs high risk, and treatment-related factors: type of treatment, treatment intensity, and duration of treatment.

Results:

During the study period, 29 pediatric patients with hematological malignancies were eligible for the study. There were 16 males and 13 females. Their age ranged between 2-16 years with the median age was 5 years. The majority were less than 6 years (58.6%). ALL was the most common diagnosis (58.6%). Eighteen (62%) patients were stratified as intermediate risk and 10 (34.4%) were high risk. The demographic data of the studied patients were shown in **table (1)**.

Twenty-six patients received intensive chemotherapy and three patients (2 with Hodgkin Lymphoma (HL), one non-Hodgkin Lymphoma (NHL)) received standard chemotherapy. The duration of therapy ranged between 5 and 41 months with a mean duration was 24.72 ± 14.78 months. Five patients (17.2%) (3 ALL, 2 HL) received radiotherapy with a mean dose was 736.13 ± 324.13 cGray as a part of their treatment plan, three of them had ALL who received prophylactic CNS radiotherapy and the other two patients had Hodgkin lymphoma received cervical and abdominal field radiotherapy.

Assessment of Igs revealed that the level of all immunoglobulins either total or measles IgM and IgG had a significant increase at three ($p<0.001$) and six months ($p<0.001$) after finishing treatment compared to their baseline levels. **Table (2).**

Compared to the normal reference value, a significant lower IgM and IgG levels among the study group at finishing treatment ($P <0.001$) and a significant lower IgG level at three months and six months after finishing treatment ($P=<0.001$) were reported, **table (2)**. On the other hand, the baseline measles IgM showed borderline higher values than normal reference values ($P=0.059$) while measles IgG showed a higher value compared to the normal reference value ($P=<0.001$). As these immunoglobulins increased during the follow-up period, both measles IgM & IgG showed significantly higher values compared to normal reference values at three and six months after finishing ($P=<0.001$).

Immunoglobulin levels in the studied patients based on:

1. **Patients-related factors:**

There were insignificant differences in the levels of all the studied immunoglobulins at the three time points ($P > 0.05$) and patients related factors (e.g., age & sex)**.**

2. **Disease diagnosis-related factors:**

On the other hand, disease diagnosis significantly affected the level of different immunoglobulins. A significantly high specific measles IgG at 6 months among patients with lymphoma (90.28±24.61) vs those with leukemia (69.74±15.34) ($P=0.019$) was noticed. Also, there was a significantly high total IgG level at six months in patients stratified as high risk than those stratified as intermediate risk (594.78 ± 165.12 vs 361.61 ± 159.64 respectively $P=0.008$). **Table (3).**

3. Treatment-related factors:

Measles IgG levels at three-time points were significantly high in the patients who received chemotherapy for ≤ 12 months (p= <0.05). a significantly high measles IgG level at six months of treatment in patients who received standard chemotherapy (p=0.012) **table (4).**

There was an insignificant difference in the levels of all studied immunoglobulins at the three time points regarding receiving high doses of cytarabine, methotrexate, and steroid. The only exception was the significantly higher level of total IgM at 3 months in patients who received high dose methotrexate in **table (5).**

The level of total IgG was significantly higher at 6 months in patients who received radiotherapy compared to those who did not receive it (P=0.024).

Table 1: Clinical characteristics of studied patients

	N=29
Age (years)(mean±SD)	6.36 ± 4.09
Range	2-16 years
Median	5 years
Age group	
< 6 years	17 (58.6%)
≥ 6 years	12 (41.4%)
Sex	
Male	16 (55.2%)
Female	13 (44.8%)
Diagnosis	
Acute lymphoblastic leukemia	17 (58.6%)
Acute myeloid leukemia	3 (10.3%)
Non-Hodgkin lymphoma	7 (24.1%)
Hodgkin lymphoma	2 (6.9%)
Risk stratification	
Low risk	1 (3.4%)
Intermediate risk	18 (62.1%)
High risk	10 (34.5%)

SD: standard deviation.

Table 2: Total and measles IgM and IgG levels in the studied patients at three-time points

	Time of assessment			***P* value**
	At finishing	After 3 months	After 6 months	
Total IgM (mg/dl)				
Patients	44.49±20.41	57.87±38.25	74.08±42.20	< **0.001**
Normal reference	67.12	67.12	67.12	
P value	<**0.001**	0.203	0.427	
Total IgG (mg/dl)				
Patients	243.68±79.8	354.77±119.74	544.23±194.65	< **0.001**
Normal reference	570.64	570.64	570.64	
***P* value**	<**0.001**	<**0.001**	<**0.001**	
Measles IgM (u/ml)	0.12 ± 0.10	0.20 ± 0.14	0.28 ± 0.18	< **0.001**
Patients	0.047-0.082	0.047-0.082	0.047-0.082	
Normal reference	0.059	<**0.001**	<**0.001**	
P value				
Measles IgG (u/ml)				
Patients	49.84±23.86	61.35±23.86	77.44±21.38	<
Normal reference	9-11	9-11	9-11	**0.001**
P value	<**0.001**	<**0.001**	<**0.001**	

Data expressed as mean (SD). P value was significant if < 0.05. Ig: immunoglobulin, mg: milligram, dl: deciliter, ml: milliliter, u: unit. Total human IgM: normal range (2-5years: 17-227mg\dl, 6-18years: 39-228mg\dl), total human IgG: normal range (2-5years: 216-1108mg\dl, 6-18years: 443-1330mg\dl) Specific measles IgM: reference value (upper cut-off: 0.0827, lower cut-off:0.04708). Specific measles IgG: Reference value (positive cut-off >11 U/ml, zona intermedia:9-11/Uml, negative cut-off:<9U/ ml

Table 3: Immunoglobulin level in relation to disease and treatment related factors in patients with hematological malignancies at three-time points

	At finishing				After 3 months				After 6 months			
	Total IgM	Total IgG	Measles IgM	Measles IgG	Total IgM	Total IgG	Measles IgM	Measles IgG	Total IgM	Total IgG	Measles IgM	Measles IgG
Diagnosis												
Leukemia (n=19)	44.84±19.8	254.30±77.93	0.13±0.11	44.65±24.84	54.99±20.34	363.97±133.57	0.208±0.157	57.83±19.12	65.35±21.65	431.11±206.17	0.28±0.22	69.74±15.34
Lymphoma (n=10)	43.72±22.94	220.10±83.41	0.115±.09	61.36±17.64	64.25±21.26	334.33±84.38	0.195±0.104	69.19±16.16	88.63±20.87	471.44±182.76	0.27±0.11	90.28±24.61
P value	0.894	0.295	0.724	0.081	0.556	0.548	0.824	0.133	0.197	0.634	0.906	**0.019**
Risk stratification												
Intermediate risk (n=18)	44.63±20.30	227.30±65.76	0.15±0.11	51.53±25.35	61.67±45.617	331.24±131.91	0.23±0.14	60.74±18.91	79.62±51.97	361.61±159.64	0.32±0.23	76.46±20.66
High risk (n=10)	44.82±22.64	284.59±88.32	0.09±0.07	46.55±23.23	51.68±23.34	407.72 ± 79.16	0.15±0.12	63.10±20.23	67.59±24.16	594.78±165.12	0.25±0.09	81.06±23.66
P value	0.962	0.061	0.245	0.874	0.803	0.183	0.338	0.902	0.737	**0.008**	0.611	0.610

Data expressed as mean (SD). *P* value was significant if < 0.05.

Table 4. Immunoglobulin levels in relation to treatment related factors in studied patients

	At finishing				After 3 months				After 6 months			
	Total IgM	Total IgG	Measles IgM	Measles IgG	Total IgM	Total IgG	Measles IgM	Measles IgG	Total IgM	Total IgG	Measles IgM	Measles IgG
Type of chemotherapy												
Standard (n=3)	55.05±41.42	312.00±48.28	0.13±0.09	72.69±8.31	100.36±66.32	387.20±54.65	0.20±0.05	74.60±6.83	108.2±113.31	556.56±126.28	0.25±0.03	105.27±18.74
Intensive (n=26)	43.27±17.7	235.80±79.50	0.12±0.10	47.20±23.72	52.96±18.47	526.5±187.89	0.20±0.15	59.82±19.14	69.21±23.75	430.47±199.73	0.29±0.19	73.47±18.92
P value	0.353	0.119	0.940	0.079	0.400	0.629	0.976	0.202	0.138	0.304	0.740	**0.012**
Duration of chemotherapy												
≤12months (n=11)	46.07±23.72	230.47±81.22	0.09±0.08	63.56±14.48	67.51±18.50	349.25±135.00	0.21±0.14	71.94±14.14	81.23±23.34	420.72±185.99	0.28±0.11	89.77±25.43
>12months (n=18)	43.52±18.78	251.76±80.16	0.14±0.10	41.45±24.87	51.97±17.31	358.15±113.40	0.19±0.14	54.88±18.56	69.79±23.94	461.54±204.48	0.28±0.22	70.05±15.01
P value	0.751	0.496	0.146	**0.013**	0.297	0.850	0.790	**0.015**	0.532	0.630	0.969	**0.025**

Data expressed as mean (SD). *P* value was significant if < 0.05.

Table 5. Total and measles IgM and IgG serum levels in studied patients received chemotherapy

	At finishing				After 3 months				After 6 months			
	Total IgM	Total IgG	Measles IgM	Measles IgG	Total IgM	Total IgG	Measles IgM	Measles IgG	Total IgM	Total IgG	Measles IgM	Measles IgG
Use of cytarabine												
Yes (n=12)	45.16±23.98	239.68 ± 87.82	0.13±0.09	53.88±23.09	60.59±25.06	342.79 ± 131.01	0.19±0.13	64.86±13.32	73.63±49.03	395.13 ± 192.22	0.27±0.21	79.52±18.43
No (n=17)	43.55±14.90	246.30 ± 76.31	0.11±0.12	44.11±24.76	54±18.32	363.23 ± 114.48	0.21±0.15	56.38±24.30	74.98±26.40	471.78 ± 196.89	0.30±0.12	73.31±27.30
P value	0.839	0.838	0.681	0.285	0.656	0.659	0.638	0.237	0.943	0.375	0.375	0.514
Use of methotrexate												
Yes (n=23)	54.77±30.33	234.90±81.39	0.09±0.07	64.56±18.13	87.08±27.15	345.52±110.45	0.23±0.14	72.41±13.01	92.50±27.70	441.63±198.09	0.28±0.07	91.95±30.71
No (n=6)	41.81±16.88	277.33±69.27	0.13±0.10	45.99±23.99	50.24±15.82	390.23±157.18	0.20±0.14	58.47±19.15	70.40±23.72	469.27±202.75	0.28±0.20	74.54±18.75
P value	0.170	0.253	0.327	0.090	**0.033**	0.425	0.603	0.106	0.350	0.802	0.980	0.141
Use of steroid												
Yes (n=25)	48.96±22.62	242.87±83.07	0.08±0.07	58.16±19.53	64.18±29.78	351.28±107.70	0.24±0.18	69.57±15.60	42.60±3.95	458.05±196.50	0.33±0.06	73.49±30.39
No (n=4)	43.77±20.45	248.75±64.71	0.13±0.10	48.15±24.56	56.58±39.58	376.62±200.68	0.20±0.14	60.04±19.15	76.94±22.97	316.20±153.86	0.28±0.19	77.80±21.33
P value	0.645	0.894	0.369	0.463	0.729	0.702	0.502	0.354	0.280	0.335	0.697	0.791

Data expressed as mean (SD). *P* value was significant if < 0.05.

Discussion:

Several studies reported a wide variation in the time of recovery of immunoglobulin ranged from one-week post-treatment up to 5 years. Similar to our result Kantar et al., found that among their patients with leukemia significantly low levels of IgM at completion of therapy compared with those determined at 6 months [5].

In contrast, Cornelis et al. reported that IgG and IgM were subnormal only in the first week post-treatment [6]. Perkins et al. found that all studied patients suffered from persistent immune abnormalities (low level of total IgM, IgG, and measles immunoglobulins) at six months off therapy [7].

The majority of our studied patients were < 6years of age (58.6%) which is nearly similar to the age of the study group of Kosmidis et al. (77% of their patients were < 6years) and on contrary the majority of Zhang et al. studied patients were > 7years. We reported no significant difference as regards the level of the immunoglobulins between this age group and those with age equal to or older than 6 years at three-time points. This is in agreement with Kosmidis et al., Zhang et al., Volc et al., and Viana et al., all of them reported that no correlation between age and recovery of measles immunoglobulins [8-11]. Other studies by Nilsson et al., Zignol et al., and Bochennek et al. reported that younger age was associated with as a higher loss of protection against measles [12-14].

It is known that females have a stronger immune response than do males with multifactorial mechanisms including endocrine and genetic effects. Affecting immune response early in life, testosterone has an immunosuppressive effect whereas estrogen can enhance T-helper cell 1(Th1) immune response at lower doses and increases Th2 and humoral immunity at higher doses [15]. This was not the case in our findings as the sex of the patients had no effect on levels of the immunoglobulins at three time points. Similar results included the findings of Yildirim and Buyukavci and Bochennek et al. who reported that measles immune response did not affect by the sex of the patients [14,16]. However, Zignol et al. expressed that the antibody loss was associated with the female sex [13]. A larger study group and multicentral study are needed to confirm this theory.

Regarding the diagnosis, Kantar found that no immunoglobulin subclass deficiency in the children with leukemia or solid tumors at the completion of therapy and 6 months after therapy [5]. Yildirim and Buyukavci, also reported that the primary diseases had no effect on the seropositivity of measles [16].

On the other hand, Kovacs et al. and Bochennek et al. stated that patients suffering from ALL lose their humoral protection significantly more frequently compared to children with other malignancies [14,17].

According to our result, the insignificant difference was reported among patients with different hematological malignancies at different time points of evaluation except for the significantly higher specific measles IgG level at six months among patients with lymphoma compared to patients with ALL and other hematological malignancies.

We can explain this finding based on the duration of treatment received, as we found that at the same point of evaluation (at six months), specific measles IgG was significantly high among patients who received their treatment for <12 months compared to ≥12 months and this is the case when we talk about patients with lymphoma who usually finish the treatment in <12 months while patients with leukemia continue treatment for 2.5-3 years. This is agreed with Bochennek et al. who reported that patients with ALL had a higher risk of losing protective humoral immunity against measles than other malignancies which may be related to a longer duration of chemotherapy. Mustafa et al. found that duration of treatment did not affect the rate of recovery of total IgM and total IgG, similar to our results [14,18].

As regard to the effect of risk stratification, we found that patients with intermediate and those with high risk had insignificant differences in levels of total IgM and IgG and measles IgM and IgG at three-time points, except that, the total IgG level that was significantly high in high-risk patients at 6 months. Again, as most of our patients with high-risk stratification diagnosed with lymphoma, we can refer that to the shorter duration of treatment rather than stratification itself.

Similarly, Bochennek et al. stated that among patients with ALL, standard- and medium-risk patients and patients treated according to the high-risk arm did not significantly differ regarding the loss of immunity against measles [14].

According to our finding, insignificant differences as regards the levels of total and specific measles Igs were reported among all patients who received either high doses of cytarabine, methotrexate, or steroid at the three-time points. The only exception was reporting of a significantly high level of total IgM at three months after finishing treatment among patients who received high dose methotrexate. We cannot explain this as a factor that favors the immune recovery but may be an associated circumstance at this time point causing the rise of the total IgM. Up to our knowledge, there is a lack of literature studied this point.

In conclusion, patients with hematological malignancies are vulnerable to humoral immune suppression at the end of the treatment. Although the level of total IgG (as one of the indicators of humoral immunity) steadily increased after stopping treatment, it persisted low for more than six months. Duration of treatment was the main factor that affected the recovery of immunoglobulin levels. So, patients with ALL are more vulnerable to delayed immune recovery and need more careful follow-up. So, these patients need strict care during the follow-up period to prevent the occurrence of infection.

A further study with a longer duration of assessment till the complete recovery and larger cohort is needed. Also, we have to assess the need and the efficacy of re-immunization for those with delayed recovery.

The expensive cost of the kit was the limitation of our study leading to the small number of patients included in the study with a small number of each diagnosis that interferes with the detection of the effect of different diagnoses on immune recovery.

List of abbreviation:

ALL: Acute Lymphoblastic Leukemia.
AML: Acute Myeloid Leukemia.
HL: Hodgkin Lymphoma.
NHL: non-Hodgkin Lymphoma.
SD: Standard Deviation.
Th1: T-helper cell 1.

Authors' contributions: All authors made substantial contributions to the conception or design of the work, acquisition, analysis or interpretation of data.

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