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Original Article

The Impact of Chemotherapy after Pediatric Malignancy on Humoral Immunity to Vaccine-Preventable Diseases

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Abstract. ***Background/Aim:*** **The antibody titer of vaccine-preventable diseases in pediatric patients who underwent chemotherapy was assessed in order to evaluate the seroprotection after treatment and the feasibility and the efficacy of a policy of revaccination.**
Methods: **Serum antibody titers of 55 patients for hepatitis B (HBV), rubella, varicella-zoster (VZV), measles, mumps, polio viruses, *Clostridium tetani* (*C. tetani*) and *Streptococcus pneumoniae* (*S. pneumoniae*) were analysed.**
Results: **After chemotherapy, a lack of protective antibody titers against HBV, rubella, VZV, measles, mumps, polio viruses, *C. tetani,* and *S. pneumoniae* was found in 53%, 45%, 46%, 46%, 43%, 21-26%, 88% and 55% of patients, respectively. In 49 of 55 patients who were tested both before and after chemotherapy for at least a pathogen, the loss of immunity for HBV, rubella, VZV, measles, mumps, polio viruses and *C. tetani* was respectively 39%, 43%, 38%, 42%, 32%, 33%, and 80%. A low number of B-lymphocytes was associated with the loss of immunity against measles (p=0.04) whereas a high number of CD8+ T-lymphocytes was associated with the loss of immunity against VZV (p=0.03). A single booster of vaccine dose resulted in a seroprotection for HBV, rubella, VZV, measles, mumps, polio viruses, *C. tetani* and *S. pneumoniae* in 67%, 83%, 80%, 67%, 33%, 100%, 88% and 67% of patients, respectively.**
Conclusions: **We confirm that seroprotection for vaccine-preventable diseases is affected by treatment for pediatric malignancy. A single booster dose of vaccine might be a practical way to restore vaccine immunity in patients after chemotherapy.**

Keywords: Vaccination; Pediatric malignancy; Chemotherapy.

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Introduction. Vaccination is one of the mayor conquests of public health.[1] It is fundamental in preventing several diseases, which could be life-threatening. Many positive results have been achieved so far, but global commitment should remain high in this field.

Patients with malignancies have an elevated risk of infections, some of them preventable by active immunization, e. g. invasive pneumococcal diseases.[2] This augmented susceptibility is related to the immune

impairment due to the disease itself or the therapies (chemotherapy, radiotherapy).[3–5] Chemotherapy causes a transient immunodeficiency that lasts for about 6 months after the end of the treatment.[6] Moreover, in patients who undergo haemopoietic stem cell transplantation (HSCT), humoral and cellular immunity is affected by chemotherapy and radiotherapy used in the conditioning regimen, and by immunosuppressive treatment used to prevent graft rejection and graft versus host disease.[7]

International guidelines recommend revaccination from at least 3-6 months after the end of chemotherapy,[8] and from 3-6 to 12-24 months after HSCT.[9]

In this study, we assessed patients' vaccination status at the diagnosis of malignancy, comparing it to that of a healthy population. Moreover, the persistence of protective antibody titer was followed-up after the end of chemotherapy in order to apply a re-vaccination protocol and assess its efficacy in restoring vaccination immunity.

Material and Methods.

Patients. Two hundred thirty-nine patients with a diagnosis of malignancy from 2010 to October 2017 were evaluated for inclusion in the study. Eligibility criteria were patients with age < 18 years, a previous diagnosis of malignancy and being off from chemotherapy for at least 6 months. Patients who undergo HSCT were excluded from the study (n=15). The period of recruitment was from January to June 2018. To exclude the potential bias related to different schedules of vaccination or different access to vaccination programs according to the country of origin, the authors recruited only Italian patients or patients born in Italy. The final study group comprised of 55 patients. Clinical data and antibody titers at the diagnosis were obtained retrospectively, consulting electronic medical records. As part of an internal program of revaccination, each eligible patient was assessed for serologic antibodies against hepatitis B (HBV), rubella, varicella-zoster (VZV), measles, mumps, polio viruses, *Clostridium tetani* (*C. tetani*) and *Streptococcus pneumoniae* (*S. pneumoniae*), and, at the same time, the immune recovery was evaluated by counting the number of CD3+, CD4+, CD8+ and CD19+ lymphocytes. Informed consent was obtained from parents for blood sampling needed to determine the serological status for vaccine-preventable diseases after chemotherapy. Patients who were not protected against at least one disease and who were eligible (n=46) were invited to perform revaccination according to internal guidelines for vaccinations that are shown in **table 1**. Twenty-one of 46 patients (46%) were compliant with the revaccination protocol. In 10 of 21 patients (48%), the efficacy of revaccination was assessed after at least one month after immunization. Data collection was closed as of January 31st, 2019.

Serologic assays. Antibodies detection for HBV, rubella, VZV, measles, mumps, polio viruses, *C .tetani,* and *S. pneumoniae* were conducted on fresh serum samples using commercial kits and following the manufacturer's instructions. Chemiluminescence technology (CLIA) was used to detect rubella, measles, mumps, VZV IgG (Diasorin S.p.A., Saluggia, Vercelli, Italy) and HBsAg antibodies (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY, US); enzyme immuno assay (EIA) was used for *C. tetani* IgG (Diasorin S.p.A., Saluggia, Vercelli, Italy) and for *S. pneumoniae* IgG (The Binding Site Group Ltd, Birmingham, UK); neutralization assay, according to

Table 1. Vaccination Protocol of the Pediatric Hematology and Oncology Unit, Verona.

Vaccine	After chemotherapy
Tetanus-diphtheria-acellular pertussis-polio- haemophilus-b-hepatitis B	Never vaccinated, start vaccination program from the beginning, 6-12 mo. after treatments. If previous only one dose, restart vaccination program from the beginning, 6-12 mo. after treatments. If 2 or 3 doses of vaccine, complete vaccination program, 6-12 mo. after treatments. If completed vaccination program, perform booster-dose 6-12 mo. after treatments.
MMR-V	Never vaccinated, start vaccination program from the beginning, 12 mo. after treatments. If previous only one dose, restart vaccination program from the beginning, 12 mo. after treatments. If completed vaccination program, perform booster-dose 12 mo. after treatments.
Streptococcus pneumoniae	Never vaccinated, start vaccination program from the beginning, 6-12 mo. after treatments. If previous only one dose, restart vaccination program from the beginning, 6-12 mo. after treatments. If 2 doses of vaccine, complete vaccination program, 6-12 mo. after treatments. If completed vaccination program, perform booster-dose 6-12 mo. after treatments.
Neisseria meningitidis	Never vaccinated, start vaccination program from the beginning, 6-12 mo. after treatments. If previous only one dose, complete vaccination program, 6-12 mo. after treatments. If completed vaccination program, perform booster-dose 6-12 mo. after treatments.
Human papillomavirus	Same recommendations of tetanus-diphtheria-acellular pertussis-polio- Hepatitis B virus according to the country schedule.
Inactivated influenza	From 3-6 months after treatments, in the recommended period of the year.

MMR-V, measles, mumps, rubella, varicella vaccine.

Table 2. Demographic and clinical characteristics of study patients.

	Hematological malignancies	Solid tumors	Total
N. of patients (%)	32 (58.2%)	23 (41.8%)	55
Gender (M/F)	21/11	16/7	37/18
Median age (years)	5.4 (0.76-16.6)	7.1 (0.44-17.7)	5.9 (0.44-17.7)
Diagnosis	ALL		20
	HL		5
	AML		3
	NHL		3*
	Hemangioendothelioma		1
		CNS tumors	7
		Wilms tumor	6
		Rhabdomyosarcoma	4
		Neuroblastoma	1
		Osteosarcoma	3
		Hepatoblastoma	1
		Germ-cell tumor	1
Interval time from diagnosis to assessment (median, range in months)	0.03 (0-2.5)	0.1 (0-5.7)	0.03 (0-5.7)
Interval time from the end of CT to assessment (median, range in months)	20.5 (3.4-68.6)	34.2 (7.3-83.6)	25.8 (3.4-83.6)

*1 patient received Rituximab (2 doses, last dose 10.5 mo. from assessment). M, male; F, female; CT, chemotherapy; ALL, acute lymphoblastic leukemia, HL, Hodgkin lymphoma; AML, acute myeloid leukemia; NHL, non-Hodgkin lymphoma; CNS, central nervous system.

WHO guidelines, was used for poliovirus. Results were interpreted as positive, negative or undetermined according to kit instructions. Positive results were considered as follow: HbsAg antibodies > 12 mUI/ml, rubella IgG $\geq$ 10 UI/mL, VZV IgG $\geq$ 135 mUI/mL, measles IgG $\geq$ 16,5 AU/mL, mumps IgG $\geq$ 9 AU/mL, *C. tetani* IgG $\geq$ 0,51 UI/mL, poliovirus IgG $\geq$ 1:8. For *S. pneumoniae* were considered positive results IgG titers >35 mg/L, in accordance with WHO recommendation.[10] Specifically, the kit used measures antibody responses to pneumococcal vaccines incorporating 23 polysaccharides isolated from *S. pneumoniae*.

Statistical analysis. Collected data were analyzed using descriptive statistics: median and range for continuous variables, absolute frequency, and percentages for categorical or dichotomous variables.

Differences of quantitative variables between groups were texted using the non-parametric Kruskal-Wallis test, whereas categorical variables using the Chi-squared test or Fisher's exact test.

The following variables were tested in univariate analysis for the loss of protective serum antibody titers: sex, type of diagnosis, age at diagnosis, time from the end of chemotherapy.

A P-value of <0,05 was considered statistically significant. Analysis was conducted using the statistical software SAS, 9.4 version (Statistical Analysis Software, SAS Institute Inc.).

The term *lack of immunity* was used for patients with non-protective antibody titers if they were tested after chemotherapy. The term *loss of immunity* was used for patients tested pre- and post- treatment and had a change of the antibody level from positive to negative. Seroprotection was defined by any level of antibody positivity, including a borderline positivity with an undetermined titer.

Results. The main demographic and clinical characteristics of patients are shown in **table 2**.

Antibody titers at diagnosis. At diagnosis, the complete serological panel of antibodies against HBV, rubella, VZV, measles, mumps, polio viruses, and *C. tetani* was available only for 11 of 55 patients, whereas 4 patients did not perform any antibody determination. The most missing data were antibodies against poliovirus (available only for 22 patients) and *C. tetani* (available for 15 patients). In **table 3**, data of seroprotection in the study population at the diagnosis (median age: 5.9 years) were compared to regional vaccination coverage

Table 3. Seroprotection of study population at the diagnosis and comparison to vaccination coverage of healthy population of the same median age.[11]

Pathogen	Seroprotection of study population (%)	VC of healthy population (%)
HBV	34/45 (76)	95
Rubella virus	36/42 (86)	89
VZV	31/42 (74)	83
Measles virus	39/43 (91)	89
Mumps virus	36/43 (84)	89
Poliovirus		
Serotype 1	16/17 (94)	90
Serotype 2	17/17 (100)	90
Serotype 3	17/17 (100)	90
C. tetani	6/13 (46)	91

VC, vaccination coverage; HBV, hepatitis B virus; VZV, varicella-zoster virus; C. tetani, Clostridium tetani.

(VC) in a healthy population of at the latest 8 years old.[11]

Some patients lack protective immunity at diagnosis, in detail, 11 patients (24%) for HBV, 6 (14%) for rubella virus, 11 (26%) for VZV, 4 (9%) for measles virus, 7 (16%) for mumps virus, 1 (6%) for poliovirus and 7 (54%) for *C. tetani*. The lack of seroprotection was related to the fact that patients were not vaccinated in 1/11 for HBV, 2/6 for rubella virus, 5/11 for VZV, 2/4 for measles virus, and 2/7 for the mumps virus.

Lack of protective serum antibody titers after chemotherapy. Fifty-five patients assessed the antibody titers after a median time of 26 months from the end of chemotherapy. The rate of the lack of protective serum antibody titers for HBV, rubella, VZV, measles, mumps, polio viruses, *C. tetani* and *S. pneumoniae* is presented in **table 4**. Data differ by type of vaccine and underlying malignancy, ranging from 27-36% for poliovirus to 89% for *C. tetani* in the group with hematological malignancies and from 8% for poliovirus to 85% of patients for *C. tetani* in solid tumors group.

Loss of protective serum antibody titers after chemotherapy. In patients tested both before and after chemotherapy, rates of protective antibody titers loss for HBV, rubella, VZV, measles, mumps, polio viruses, and *C. tetani* are summarized in **table 5**. Rates vary depending on vaccine type: from 32% of patients for mumps virus to 80% for *C. tetani*.

Univariate analysis for the loss of protective serum antibody titer is given in **table 6**. No factor was statistically significant.

The comparison between the number of CD3+, CD4+, CD8+ and CD19+ lymphocytes determined

Table 4. Rates of lack of protective serum antibody titer in patients tested after chemotherapy.

Pathogen	N° of patients	Hematological malignancies (%)	Solid tumors (%)	Total (%)
HBV	47	14/30 (47)	11/17 (65)	25/47 (53)
Rubella virus	40	14/26 (54)	4/14 (29)	18/40 (45)
VZV	41	15/28 (54)	4/13 (31)	19/41 (46)
Measles virus	41	13/27 (48)	6/14 (43)	19/41 (46)
Mumps virus	40	13/26 (50)	4/14 (29)	17/40 (43)
Poliovirus type 1	34	8/22 (36)	1/12 (8)	9/34 (26)
Poliovirus type 2	34	7/22 (32)	1/12 (8)	8/34 (24)
Poliovirus type 3	34	6/22 (27)	1/12 (8)	7/34 (21)
C. tetani	40	24/27 (89)	11/13 (85)	35/40 (88)
S. pneumoniae	31	11/15 (73)	6/16 (38)	17/31 (55)

HBV, hepatitis B virus; VZV, varicella-zoster virus; C. tetani, Clostridium tetani; S. pneumoniae, Streptococcus pneumoniae.

Table 5. Rate of loss of protective antibody titers after chemotherapy in patients tested both before and after chemotherapy.

Pathogen	N° of patients	Total (%)
HBV	31	12/31 (39)
Rubella virus	28	12/28 (43)
VZV	24	9/24 (38)
Measles virus	31	13/31 (42)
Mumps virus	28	9/28 (32)
Poliovirus	12	4/12 (33)
C. tetani	5	4/5 (80)

HBV, hepatitis B virus; VZV, varicella-zoster virus; C. tetani, Clostridium tetani.

Table 6. Univariate analysis of factors associated with loss of immunity after chemotherapy.

	HBV	Rubella virus	VZV	Measles virus	Mumps virus	Poliovirus	*C. tetani*
Sex (%) M vs F	8/19 (42) vs. 4/12 (33)	9/19 (47) vs. 3/9 (33)	7/16 (44) vs. 2/8 (25)	9/22 (41) vs. 4/9 (44)	7/20 (35) vs. 2/8 (25)	2/6 (33) vs. 2/6 (33)	3/3 (100) vs. 1/2 (50)
p	0.7	0.7	0.7	1	1	1	0.4
Type of diagnosis (%) HE vs ST	8/22 (36) vs. 4/9 (44)	10/20 (50) vs. 2/8 (25)	9/19 (47) vs. 0/5 (0)	11/23 (48) vs. 2/8 (25)	8/20 (40) vs. 1/8 (13)	3/11 (27) vs. 1/1 (100)	4/5 (80) vs. -
p	0.7	0.4	0.1	0.4	0.2	0.3	NA
Age at diagnosis (%) <7.4 vs >7.4 y	7/16 (44) vs. 5/15 (33)	6/13 (46) vs. 6/15 (40)	5/8 (63) vs 4/16 (45)	4/15 (27) vs. 9/16 (56)	4/13 (31) vs. 5/15 (33)	3/7 (43) vs. 1/5 (20)	2/2 (100) vs. 2/3 (67)
p	0.6	0.7	0.1	0.1	1	0.6	1
Time from the end of CT (%) <6 vs 6-12 vs >12 mo.	0/1 (0) vs. 1/9 (11) vs. 11/21 (52)	1/2 (50) vs. 3/9 (33) vs. 8/17 (47)	1/2 (50) vs. 4/7 (57) vs. 4/15 (27)	0/2 (0) vs. 2/9 (22) vs. 11/20 (55)	0/2 (0) vs. 2/8 (25) vs. 7/18 (39)	1/1 (100) vs. 0/6 (0) vs. 3/5 (60)	- vs. 2/2 (100) vs. 2/3 (67)
p	0.05*	0.7*	0.2*	0.07*	0.4*	0.2*	NA
Total	31	28	24	31	28	12	5

HBV, hepatitis B virus; VZV, varicella-zoster virus; C. tetani, Clostridium tetani; M, male; F, female; HE, hematological malignancies; ST, solid tumors; CT, chemotherapy; NA, not applicable. *The comparison was performed between <=12 mo. vs >12mo., because of the too low sample size.

Table 7. Comparison between lymphocyte subpopulations in peripheral blood of study patients after chemotherapy and healthy controls.[12]

	CD3+ median (range)	CD4+ median (range)	CD8+ median (range)	CD19+ median (range)
Normal values for age (5-10 years old)	1.9 (0.7-4.2)	1 (0.3-2)	0.8 (0.3-1.8)	0.5 (0.2-1.6)
Study population	1.7 (0-5)	0.8 (0-2.7)	0.5 (0-2.4)	0.5 (0-1.7)

after chemotherapy and average values for age, i.e., 5-10 years old,[12] is shown in **table 7**.

In univariate analysis, a lower number of B-lymphocytes resulted significantly associated with the loss of protective antibody titer for measles virus, p=0.04, whereas a higher number of CD8+ T-lymphocytes was significantly associated with the loss of antibody protection for VZV, p=0.03.

Antibody titers after vaccination protocol application. Revaccination with a single-shot vaccination boost of 10 patients who underwent chemotherapy obtained the restoration of protective serum antibody level in 2 out of 3 patients for HBV, in 5 out of 6 patients for rubella virus, in 4 out of 5 patients for VZV, in 4 out of 6 patients for measles virus, in 2 out of 6 patients for mumps virus, in 8 out of 8 patients for poliovirus, in 7 out of 8 patients for *C. tetani* and in 2 out of 3 patients for *S. pneumoniae*.

Discussion. This study was part of an internal program to stimulate adherence to the revaccination protocol after treatment with chemotherapy for malignancy. The assessment of vaccination serological coverage at the diagnosis showed that several patients were not protected. In twelve out of 47 (25%) seronegative status was attributable to the fact that patients were not compliant with the national vaccination program for newborn and child because of the young age at the diagnosis of malignancy or of parental decision. This last reason was observed especially for attenuated live virus vaccine where the viral replication by vaccine strain is perceived by parents as a potential risk for recurrence of the underlying disease. On the other hand, 33 out of 47 determinations (70%) resulted in negative despite that patients were vaccinated. It may be explained by the fact that some patients did not have completed the primary cycle of vaccination by the time of the diagnosis or the vaccination was ineffective.

In this study, data of protective immunity due to vaccination were not available for every patient, especially for *C. tetani* and poliovirus. This reflects a local problem because these tests were not performed at the hospital laboratory, and, if requested by the physician in charge, the serum samples had to be sent to laboratories outside, increasing the costs.

When the rate of patient seroprotection at the diagnosis was compared to the vaccination coverage in a healthy population, significant differences were seen for HBV (respectively 76% vs. 95%), poliovirus (94-100% vs. 90%), and *C. tetani* (46% vs. 91%). We underline that seroprotection figures in the study

patients were calculated on the basis of antibody determinations, whereas in the general population, this index is based just on the administration of vaccination, irrespective of efficacy in terms of seroprotection. Therefore, the data on regional vaccination coverage for vaccines could not correspond to the efficacy of vaccination, intended as the documentation of a protective antibody titer after vaccination. Moreover, the differences could also be attributed to the small sample size. Considering the ideal immunization coverage recommended by World Health Organization in the health population to provide herd immunity, i.e., 95%, it emerged that patients' immunization coverage was far from this value, except from polio (95-100%).

One of our principal purposes was to analyze the impact of chemotherapy on vaccine humoral immunity. We demonstrated that patients were prone to loose protective antibody titer, acquired by vaccination, or in some cases by natural infection. As a result, the patients after chemotherapy are frequently not protected against vaccine-preventable diseases, and this fact can be relevant when the patients return to school or in the community. In the case of outbreaks, like the measles outbreak which affected Italy in 2017,[13] these patients would be hugely at risk.

In literature, the loss of protective antibody titers after chemotherapy is frequent, even if percentages of loss or lack of immunity vary depending on the study considered, ranging from 25-88% for measles virus, 26-88% for mumps virus, 19-88% for rubella virus,[14–16] 17-35% for VZV,[14,17] 11.6-14% for *C. tetani*,[15,18] 7% for poliovirus,[15] and 26-86% for HBV.[15,16,19,20] In patients with Acute Lymphoblastic Leukemia, non-protective antibody levels were seen in 2-80% patients for *C. tetani*, 0-38% for poliovirus, 8-71% for mumps virus, 40- 71% for measles virus and 8-28% for rubella virus.[21] Although these studies are heterogeneous, most of them were performed with patients with hematological malignancies, whereas our study included both hematological and solid tumors.

The risk factor analysis for the loss of immunity did not find any association with sex, type of diagnosis, age at diagnosis, and time from the end of chemotherapy, although we highlight that the sample was small. Interestingly, we showed that a low number of CD19+ lymphocytes was associated with the loss of protective antibody titer against measles virus. This observation is in line with the finding that patients treated with B-depleting monoclonal antibodies, such as rituximab, have lower responses to vaccination for at least 6 months after the end of treatment.[22,23] We also found that a high number of CD8+ lymphocytes is associated with the loss of immunity against VZV. This finding needs to be confirmed further.

In order to evaluate the role of the immune recovery in the persistence or the loss of vaccine immunity after therapies, the peripheral blood subpopulations of lymphocytes were assessed, and no differences were found between study patients and healthy children of the same age. We hypothesize that the re-exposure to vaccine antigens has a crucial role in vaccine immunity reconstitution in order to induce the appearance and proliferation of lymphocytes capable of mounting a specific humoral response again. For this reason, our policy was to revaccinate the patients starting from 6 months from the end of treatments. Forty-six percent of patients were compliant with this policy by the study period and this measure was associated with a seroprotection in 33-100% of patients after a single booster dose of vaccine.

Conclusions. This study confirms that the loss of humoral protection from vaccine preventable diseases is a common finding among hematological and oncological patients after chemotherapy. The practice to revaccinate the patients to re-establish individual protection and to contribute to the herd immunity has a favorable benefit/risk ratio especially for the return to community activities or for travelling. Several important issues remain to define such as the optimal timing for revaccination (6-12 months vs. other) and the type of schedule (boost vs. full repeated doses) that requires further prospective studies on a larger number of patients.

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Supplementary tables:

Supplementary table 1. Univariate analysis of the number of lymphocytes in peripheral blood and the loss of protective antibody titers after chemotherapy.

	CD3+ lymphocytes			T CD4+ lymphocytes		
Loss	**YES**	**NO**	***p***	**YES**	**NO**	***p***
HBV	1.4 (0.8-4.3)	1.4 (0-5)	ns	0.7 (0.5-1.7)	0.8 (0-2.7)	ns
Rubella virus	1.8 (0-4.3)	1.4 (1-3.1)	ns	0.8 (0-1.7)	0.8 (0.5-1.3)	ns
VZV	1.7 (0.8-3.1)	1.2 (0-2.4)	ns	0.8 (0.5-1.2)	0.6 (0-1.3)	ns
Measles virus	1.4 (0-2.6)	1.8 (1-4.3)	ns	0.7 (0-1.3)	0.9 (0.5-1.7)	ns
Mumps virus	1.7 (0.8-2.1)	1.4 (0-4.3)	ns	0.8 (0.5-1)	0.8 (0-1.7)	ns
Poliovirus	1.3	1.5 (1.1-2.4)	-	0.5	0.8 (0.6-1.2)	-
C. tetani	1.6 (1.4-1.8)	1.8	-	0.8 (0.6-0.9)	1.3	-
	T CD8+ lymphocytes			**CD19+ lymphocytes**		
Loss	**YES**	**NO**	***p***	**YES**	**NO**	***p***
HBV	0.5 (0.3-2.4)	0.5 (0-1.9)	ns	0.5 (0.3-0.9)	0.5 (0-0.9)	ns
Rubella virus	0.7 (0-2.4)	0.5 (0.3-1.7)	ns	0.5 (0-1.4)	0.5 (0-0.7)	ns
VZV	0.7 (0.3-1.7)	0.5 (0-1)	0.03	0.5 (0-0.7)	0.3 (0-1.4)	ns
Measles virus	0.5 (0-1.2)	0.6 (0.4-2.4)	ns	0.4 (0-0.5)	0.5 (0-1.4)	0.04
Mumps virus	0.6 (0.3-1.1)	0.5 (0-2.4)	ns	0.5 (0.3-0.9)	0.5 (0-0.9)	ns
Poliovirus	0.6	0.6 (0.3-0.9)	-	0.5	0.5 (0-1.4)	-
C. tetani	0.6 (0.5-0.7)	0.4	-	0.5 (0.3-0.7)	0.2	-

HBV, hepatitis B virus; VZV, varicella-zoster virus; C. tetani, Clostridium tetani; ns, difference not statistically significant.

Supplementary table 2. Presence of protective antibody titers after application of Vaccination Protocol, after chemotherapy.

Pathogen	N° of patients vaccinated	Total* (%)
HVB	5	2/3 (67)
Rubella virus	7	5/6 (83)
VZV	5	4/5 (80)
Measles virus	7	4/6 (67)
Mumps virus	7	2/6 (33)
Poliovirus	10	8/8 (100)
C. tetani	10	7/8 (88)
S. pneumoniae	4	2/3 (67)

*Single boost dose of vaccine, except for one patient who was administered two doses of tetanus vaccine. HBV, hepatitis B virus; VZV, varicella-zoster virus; C. tetani, Clostridium tetani; S. pneumoniae, Streptococcus pneumoniae.

Supplementary table 3. Vaccine immunity reconstitution in patients with lack of immunity after chemotherapy, after the application of Vaccination Protocol.

Pathogen	N° of patients vaccinated	Total* (%)
Hepatitis B	5	2/3 (67)
Rubella virus	5	3/4 (75)
VZV	3	2/3 (67)
Measles virus	5	2/4 (50)
Mumps virus	5	0/4 (0)
Polio type 1	2	2/2 (100)
Polio type 3	2	1/1 (100)
C. tetani	9	6/7 (86)
S. pneumoniae	2	1/1 (100)

*Single boost dose of vaccine, except for one patient who was administered two doses of tetanus vaccine; HBV, hepatitis B virus; VZV, varicella-zoster virus; C. tetani, Clostridium tetani; S. pneumoniae, Streptococcus pneumoniae.