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Vaccine Efficacy of Hepatitis A and B in Pediatric Oncology Patients

Deniz Kızmazoğlu, MD[1]
Dilek Orbatu, MD[2]
Demet Alaygut, MD[3]
Oya Baltalı, MD[4]

[1] Tepecik Training and Research Hospital Department of Pediatric Oncology.

[2] Tepecik Training and Research Hospital Department of Pediatrics.

[3] Tepecik Training and Research Hospital Department of Pediatric Nephrology.

[4] Tepecik Training and Research Hospital Department of Social Pediatrics.

Correspondence:
Dilek Orbatu, MD
Tepecik Training and Research Hospital
Department of Pediatrics
1140/1 street No: 1
Yenişehir /İzmir

Phone: +90 505 755 65 79
Email: drdilekorbatu@gmail.com

Background: To investigate the factors affecting pre-, and post-treatment hepatitis A and B vaccine antibody titers and the responses to vaccine in the post-treatment period of pediatric patients with the diagnosis of cancer.

Objective: The archival data of the patients with an oncologic diagnosis followed up in the Pediatric Oncology and Healthy Children Polyclinics of Tepecik Training and Research Hospital between 2011 and 2018 were retrospectively reviewed. The age at diagnosis, sex, primary diagnosis, average number of days elapsed between the diagnosis, and initiation of chemotherapy, antibody titers at the time of diagnosis, preoperative status of Hepatitis B, Hepatitis A vaccine and Hepatitis B Ig administration , duration of treatment and titers in the second assessment after treatment were evaluated.

Material & methods: Medical files of a total of 123 cases including 74 (60%) male patients could be accessed. The mean age of the patients at diagnosis was 98.2 ± 66.2 (0.5-214) months. The primary diagnoses were leukemia in 50 (40.7%) lymphoma in 27 (22.0%) and solid tumors in 46 (37.4%) patients. The mean duration of treatment was 14.8 ± 9.0 (1.54-39.6) months. Serologically post-treatment HB-negativity was comparatively higher in male patients who were HB-positive before, but HB-negative treatment after treatment ($p = 0.039$). In cases with hepatitis A, a significant correlation was detected duration of treatment was prolonged ($p = 0.021$).

Results: Medical files of a total of 123 cases including 74 (60%) male patients could be accessed. The mean age of the patients at diagnosis was 98.2 ± 66.2 (0.5-214) months. The primary diagnoses were leukemia in 50 (40.7%), lymphoma in 27 (22.0%) and solid tumors in 46 (37.4%) patients. The mean duration of treatment was 14.8 ± 9.0 (1.54-39.6) months. Serologically post-treatment HB - negativity was comparatively higher in male patients who were HB-positive before, but HB-negative treatment after treatment ($p = 0.039$). In cases with hepatitis A, a significant correlation was detected duration of treatment was prolonged ($p = 0.021$).

Conclusion: Antibody loss was found to be more prominent in male gender for Hepatitis B vaccination. For hepatitis A, antibody loss was more pronounced with treatment duration.

Keywords: hepatitis A, hepatitis B, pediatric oncology, vaccine

Introduction

In the last century, rates of morbidity and mortality related to prevalent infectious diseases in developed countries have decreased significantly thanks to advances in vaccination practice [1]. Today, vaccination programs represent a universally recognized tool both to prevent the spread of many infectious agents and to reduce death and disability worldwide [1]. Definitive eradication of certain vaccine-preventable diseases has been thus achieved against diseases such as smallpox worldwide and polio in the United States and Europe [2]. Vaccination programs are constantly updated. The use of novel vaccines such as herpes, varicel-

la-zoster virus (VZV), pneumococcal, meningococcus C, and human papilloma virus (HPV) has been introduced in the last two decades [3].

Nowadays, pediatric malignant diseases are the second most common cause of death in developed countries. Survival rates have increased significantly in the last 30 years thanks to multidisciplinary approach based on chemotherapy, and surgery, radiotherapy, hematopoietic stem cell transplantation and supportive treatments [4]. An important disadvantage of chemotherapy is that it suppresses immunity which persists up to 6-12 months after end of the treatment [5]. It adversely affects the effectivess of these vaccines which may be due to a complete or partial loss of protective serum antibody titers or a combination of other immune deficiencies such as the presence of functional asplenia [6]. In general, patients treated for pediatric malignancies are not at high risk except for patients with splenectomy or functional asplenia when compared to healthy population. However, there is a limited number of literature data on serious conditions caused by insufficiency of vaccine against Haemophilus influenzae or Streptococcus pneumoniae, measles and rubella in cases where long-term humoral response is defective [7]. Therefore, actual need for vaccines is still an important issue in pediatric cancer patients during and after treatment. The aim of this study was to investigate the Hepatitis B and Hepatitis A vaccine antibody titers, the vaccine or immunoglobulin treatments administered before and after treatment of pediatric cancer patients, and the factors affecting the vaccine response in the post-treatment period.

Material & Methods

The study was performed by retrospectively examining the file data of children with oncological diagnosis followed up in Pediatric Oncology and Healthy Children Polyclinics of Tepecik Training and Research Hospital of Health Sciences University between 2011-2018. Age, gender, primary diagnosis, average number of days elapsed between diagnosis and initiation of chemotherapy, anti HBs and anti HAV titers at the time of diagnosis, administration status of Hepatitis B and Hepatitis A vaccines and Hepatitis B Ig before treatment, duration of treatment were evaluated and second assessments of Anti-HBs titer and anti HAV Ig parameters were performed local ethics committee approval was obtained. It was taken into consideration that the patients to be included in the study group were between 0-18 years of age and that cancer treatments were completed at least 6 months before collection of data. All patients screened for hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBcAb), hepatitis B e-antigen (HBeAg) and anti Hepatitis A Ig (anti HAV Ig) were taken into consideration. In order to maintain the integrity and validity of the data, only patients with a complete clinical and medical data record set that were found to be in remission were included in the study sample. Patients who were receiving active cancer treatment, those who had anticancer treatment, recently vaccinated patients or individuals who recently received blood transfusions or IVIG treatment were not included in the study. In addition, patients with active hepatitis B infection, cases previously diagnosed with immunodeficiency or having low immunoglobulin G (Ig G) levels for their age were excluded from the study. Before initiation of cancer treatment, serologic tests for hepatitis A, and B had to be performed in all patients and their primary HBV vaccinations had to be realized according to National immunization program of Republic of Turkey (three doses ie. at birth, 2 and 6 months). All seronegative patients (HbsAb <10 mIU/ml) received hepatitis B Ig IM prior to treatment according to the protocol of the center. Hepatitis A vaccine was administered to patients with negative hepatitis A serology. All patients were reevaluated with serologic tests at least 6 months after the end of the treatment, and those with missing data were excluded from the study. Antibody titers were evaluated with enzyme-linked immunoassay. Patients with HBsAb titers of <10 mIU / ml for hepatitis B and negative results for hepatitis A were considered to be seronegative. Statistical Package for Social Sciences (SPSS) version 24.0 for Windows (SPSS, Inc., Chicago, IL, USA) was utilized for pertinent data analysis. The Mann-Whitney U test and chi-square test were used to compare variables and p value of <0.05 was considered to be statistically significant.

Results

Medical files of a total of 123 cases including 74 (60%) male, and 49 (40%) female patients could be accessed. The mean age of the patients at diagnosis was 98.2 ± 66.2 (0.5-214) months. The primary diagnoses were leukemia in 50 (40.7%) lymphoma in 27 (22.0%) and solid tumors in 46 (37.4%) patients. The mean time interval up to treatment was 9.3 ± 26.2 (1-172) days. Hepatitis B IgG was given to all 41 patients who had negative hepatitis B (HB) serology before the treatment. Hepatitis A vaccination had been performed in anti-HAV IgG negative 65 cases. The mean duration of treatment was 14.8 ± 9.0 (1.54-39.6) months. (Table 1). Hepatitis B and Hepatitis A patients whose serologic tests were achieved were divided into four groups. Group 1 consisted of patients with negative serologies both before and after treatment, Group 2 comprised patients with negative, and positive serologies before and after treatment, respectively.

Table 1. General features of patients.

Feature	N (%)
Gender	
Male	74 (60.2%)
Female	49 (39.8%)
Age of at diagnosis	98.2 ± 66.2 (0.5-214) months
Primary diagnosis	
Leukemia	50 (% 40.7)
Lymphoma	27 (%22.0)
Solid tumor	46 (%37.4)
Duration of treatment	9.3 ± 26.2 (1-172) days
Pre-treatment serology	
Hep B (-)	41 (%37.3)
Hep A (-)	65 (%52.8)
Duration of treatment	14.8 ± 9.0 (1.54- 39.6) months

Table 2. Definition of groups.

Group 1	BT (-) / AT (-)
Group 2	BT (-) / AT (+)
Group 3	BT (+) / AT(-)
Group 4	BT (+) / AT (+)

AT: after treatment , BT: before treatment

Patients with positive, and negative serologies before, and after treatment were included in Group 3. Group 4 had patients with positive serologies before, and after treatment (Table 2). Gender, primary diagnosis and duration of treatment were evaluated in these groups. The distribution of the groups is shown in Table 3. There was a significant difference for hepatitis B in favour of male gender in Group 3 (p = 0.039). In Group 4, the positivity rate was significantly higher in girls. There was no significant relationship between duration of treatment and primary diagnosis. The primary diagnosis for hepatitis A was not significantly correlated with gender, but the rate of negativity was significant as the duration of treatment was prolonged (p = 0.021).

Discussion

The aim of this study was to evaluate the vaccine responses and the factors affecting this response in children with established diagnosis of cancer. Since there are still no clear answers on this subject, it presumably has contributed to the literature. Acquired Hepatitis B infection or reactivation of HBV in patients undergoing malignancy treatment is a known complication in those receiving cytotoxic or immunosuppressive therapy. These conditions have been also reported in HbsAg positive patients after chemotherapy and transplantation [8]. Although there are many vaccines in the national vaccination program, two serologies with the most commonly analyzed and easily accessible data have been evaluated in order to introduce a certain standardization. Although there are no clear answers about the routine to be followed after chemotherapy, some studies have reported that booster vaccination should be administered 6 months after chemotherapy. Another study proposed this practice 12 months after chemotherapy [9,10]. However, Fioredda et al. stated that the vaccination scheme should be maintained after treatment in this group of children as in normal healthy individuals [11]. Guidelines for the immunization of children after chemotherapy also vary among countries. US CDC [1993] has recommended re-vaccination 2 weeks before the initiation or at least 3 months after chemotherapy [12]. UK RCPCH [2002] recommends vaccination of seronegative high-risk cases only [13]. The updated Australian guidelines for vaccination recommend a single adjuvant dose for HBV after chemotherapy if the patient has completed primary vaccination at the time of diagnosis [14]. Esposito et al. however, recommended two booster doses for HBV at 3-month intervals after chemotherapy in the presence of epidemiological risk without considering any other factor [15]. In our study, all patients who were seronegative prior to chemotherapy were vaccinated with Ig for HBV and HAV for vaccination with the application almost in compliance with CDC recommendations and chemotherapy was initiated. After chemotherapy, serology was re-evaluated at the earliest 6 months and seronegative ones were vaccinated. Hepatitis B and Hepatitis A seronegativities were detected in 33.3% and 52.4% of the patients in this study group, respectively. In their study Fayea NY et al. found that HBV seronegativity rate of 86% [16]. In the literature, there are different reported results related to seropositivity after chemotherapy. Seropositivity for HBV has been reported to be between 80-84% at the end of treatment in children with acute lymphoblastic leukemia [17, 18]. Another study reported 50-60% loss of seropositivity in 50-60% of cases [19]. Although Hepatitis B vaccination has been included in the national vaccination program since 1998 and Hepatitis A vaccination since 2012, considering the age at diagnosis of the patients was 98 months, they should have all completed the primary vaccination program. However, it was tragic that the seronegativity before treatment ranged between 33% and 52%. This cannot be explained alone by incomplete implementation of national vaccination program. Because the country's ministry of health has strict controls and sanctions related to vaccination program. Surgical procedures, blood transfusions, immunosuppressive therapies, as well as personal immune response are thought to play an important role. Another known fact is that patients respond differently to chemotherapy. It is not possible to generalize these recommended vaccinations to all patients after chemotherapy. The main purpose of this study was to determine the parameters

Table 3. Distribution of patients by groups and related situations.

Disability	Hepatitis B					Hepatitis A				
	Group 1	Group 2	Group 3	Group 4	p	Group 1	Group 2	Group 3	Group 4	p
Primary diagnosis										
Leukemia	2	13	13	22	0,252	6	21	13	10	0,193
Lymphoma	3	8	7	9		2	14	3	8	
Solid tumour	8	7	9	22		5	23	3	15	
Gender										
Male	8	18	23	25	*0,034*	8	36	11	19	0,972
Female	5	10	6	28		5	22	8	14	
Duration of treatment	9.82 ± 6.3	13.3 ± 8.9	17.6 ± 9.4	15.2 ± 9.08	0,230	93,5 ± 53	106.2 ± 67	56.5 ± 44.6	110.3 ± 72.1	*0,021*

that would affect the differences in this response. The effect of cancer treatment on immunization by vaccination is not clearly known. Many different factors may affect antibody titers. In previous studies, genetic predispositon, human leukocyte antigen (HLA) haplotypes, interleukin genotypes, and polymorphisims in cytokines or cytokine receptors were found to be effective in generating lower immunogenic response to HBV vaccine [20]. For example, in patients with atopic dermatitis and psoriasis, both these immunological factors and the excessive inflammation caused by the underlying disease are known to inhibit the increase in anti HBs titers. Moreover, although atopic dermatitis is a T helper 2 (TH2) disease and psoriasis is a T helper 1 (TH1) disease, the response is similar. In the presence of a cancer, it is not possible to understand potential changes in the immune system, tumor cell behavior and their relationship with the genetic immunologic, genotypic characteristics of the individual. Therefore, uncertainties remain about prediction of vaccine responses and their potential interaction with the treatment. There are many studies on the factors affecting vaccine antibody titers after treatment. In a serological study, Zignol M et al. detected rates of antibody negativities for hepatitis B, measles, mumps, rubella, tetanus and polio in 46%, 25%, 26%, 24%, 14% and 7% of the patients respectively. Negativities for rubella, mumps and tetanus antibodies were correlated with age and measles antibody negativities with age and gender. Antibody loss was found to be more prominent in younger patients and girls [10] In their study, Karaman S et al. could not find a any correlation between post-treatment antibody titers , age and sex [21]. In contrast to the aforementioned two studies, in this study the rate of antibody negativity in male gender was found to be higher only for Hepatitis B antibody responses. The relationship with age was not determined for both Hepatitis A and Hepatitis B antibody responses. When evaluated in terms of the relationship with the type of the present disease, hepatitis B antibody titers decreased mostly in sarcoid patients even below the protective level in 64% of the patients [22]. In a study by Karaman S et al. antibody loss was found to be higher in children with leukemia [21]. In this study, primary diagnosis was not important as for both antibody titers. We think that an additional contribution of this study to the literature will be related to hepatitis A vaccination and vaccine response. Although many studies have been performed on this issue, we did not find any study in which Hepatitis A was evaluated in children with cancer. When hepatitis A vaccination was evaluated, it was found that age, sex, primary diagnosis did not affect the response to vaccination after treatment, but the rate of negativity for Hepatitis A was significantly higher as the duration of anticancer treatment was prolonged . The limitation of this study was that it was a single-center, retrospective study performed with a small sample group. In addition, the types of chemotherapy that patients received were not specified. It is known that viral reinfection is more prominent with some chemotherapy agents and serology may be affected. In conclusion, although there are guidelines on vaccination programs that have already been identified and recommended for children with the diagnosis of cancer, we have seen that individual differences are at the forefront due to many factors that we do not know.

Conclusion

In conclusion, male sex and long-term exposure to hepatitis seem to be risk factors for Hepatitis B antibody responses, prospective multicenter, studies involving genotypic characteristics of the patients with established, and detailed immunological maps, times, and routes of vaccination where immune responses after each vaccination are evaluated should be conducted. Perhaps this protocol will be told us by an artificial intelligence to be developed in the future.

References

1. Cesaro S, Giacchino M, Fioredda F et al. Guidelines on vaccinations in paediatric haematology and oncology patients. Biomed Res Int. 2014;2014:707691
2. S. W. Roush, T. V. Murphy, M. M. Basket et al. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States Journal of the American Medical Association 2007; 298: 2155-2163
3. CDC, "Recommended immunization schedules for persons aged 0–18 years-United states 2010," Morbidity and Mortality Weekly Report 2009; 57: 51-52
4. Principles of multimodal therapy, in Principles and Practice of Pediatric Oncology, P. A. Pizzo and D. G. Poplack, Eds., Lippincott, Philadelphia, Pa, USA, 2011.
5. T. Ek, L. Mellander, B. Andersson, and J. Abrahamsson, Immune reconstitution after childhood acute lymphoblastic leukemia is most severely affected in the high risk group," Pediatric Blood and Cancer 2005; 44 : 461–468
6. R. Meisel, A. M. Toschke, C. Heiligensetzer, D. Dilloo, H.- J. Laws, and R. Von Kries, "Increased risk for invasive pneumococcal diseases in children with acute lymphoblastic leukaemia," British Journal of Haematology 2007; 137: 457–460
7. T. Lehrnbecher, R. Schubert, M. Behl et al., "Impaired pneumococcal immunity in children after treatment for acute lymphoblastic leukaemia," British Journal of Haematology, 2009; 147:700–705
8. Abdalla M, Hamad T. Hepatitis B Virus Seroprevalence Among Children With Cancer in Sudan. Pediatr Blood Cancer 2016 ;63:124-6.
9. Ayerbe MC, Pérez-Rivilla A, ICOVAHB group. Assessment of long-term efficacy of hepatitis B vaccine. Eur J Epidemiol 2001 ; 17: 150–156
10. Zignol M, Peracchi M, Tridello G, Pillon M, Fregonese F, D'Elia R et al. Assessment of humoral immunity to poliomyelitis, tetanus, hepatitis B, measles, rubella, and mumps in children after chemotherapy. Cancer 2004; 101:635–641
11. Fioredda F, Plebani A, Hanau G, Haupt R, Giacchino M, Barisone E et al. Re-immunisation schedule in leukaemic children after intensive chemotherapy: a possible strategy. Eur J Haematol 2005; 74:20–23.
12. Centers for Disease Control and Prevention. Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins in persons with altered immunocompetence. MMWR Recomm Rep 1993; 42:1–18
13. Royal College of Paediatrics and Child Health (RCPCH) (2002) Immunization of the immunocompromised child: best practice statement. RCPCH; https://www.bspar.org.uk/DocStore/FileLibrary/PDFs/Immunisation%20of%20the%20Immunocompromised%20Child.pdf.
14. Australian Immunization Handbook 10th edition (2016) NHMRC. Canberra. Australia. Available athttp://www.immunise.health.gov.au/ internet/immunise/publishing.nsf/Content/7B28E87511E08905 CA257D4D001DB1F8/$File/Aus-Imm-Handbook.pdf
15. Esposito S, Cecinati V, Brescia L, Principi N. Vaccinations in children with cancer. Vaccine 2010; 28:3278–3284
16. Fayea NY, Kandil SM, Boujettif K, Fouda AE. Assessment of hepatitis B virus antibody titers in childhood cancer survivors. Eur J Pediatr. 2017;176:1269-1273
17. Fioredda F, Plebani A, Hanau G, Haupt R, Giacchino M, Barisone E et al. Re-immunisation schedule in leukaemic children after intensive chemotherapy: a possible strategy. Eur J Haematol 2005; 74:20–23
18. Shams Shahemabadi A, Salehi F, Hashemi A, Vakili M, Zare F, Esphandyari N, Kashanian S. Assessment of antibody titers and immunity to hepatitis B in children receiving chemotherapy. Iran J Ped Hematol Oncol 2012; 2:133–139
19. Brodtman DH, Rosenthal DW, Redner A, Lanzkowsky P, Bonagura VR. Immunodeficiency in children with acute lymphoblastic leukemia after completion of modern aggressive chemotherapeutic regimens. J Pediatr 2005;146:654–661
20. Patel DP, Treat JR, Castelo-Socio L . Decreased Hepatitis B vaccine response in pediatric patients with atopic dermatitis, psoriasis, and morphea. Vaccine. 2017;16;35(35 Pt B):4499-4500.
21. Karaman S, Vural S, Yildirmak Y, Urganci N, Usta M. Assessment of hepatitis B immunization status after antineoplastic therapy in children with cancer. Ann Saudi Med. 2011;31:573-6.
22. Yu J, Chou AJ, lennox A, Kleiman P, Wexler LH, meyers PA et al. Loss of antibody titers and effectiveness of revaccination in post-chemothreapy pediatric sarcoma patients. Pediatr Blood Cancer 2007; 49: 656-60