RESEARCH ARTICLE
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Waning of Humoral Immunity to Vaccine-Preventable Diseases in Children Treated for Acute Lymphoblastic Leukemia: A Single-Center Retrospective Cross-Sectional Analysis

Akut Lenfoblastik Lösemi Tedavisi Gören Çocuklarda Aşıyla Önlenebilir Hastalıklara Karşı Humoral Bağışıklığın Azalması: Tek Merkezli Retrospektif Kesitsel Analiz

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Abstract
Objective: The survival rates of children with acute lymphoblastic leukemia (ALL) have improved over the years, but infections remain a significant cause of morbidity and mortality. Chemotherapy has a range of harmful side effects including the loss of protective antibodies against vaccine-preventable diseases. The objective of this study was to evaluate the serological status of pediatric ALL cases before and after the intensive chemotherapy.
Materials and Methods: Children treated and followed up for ALL at Dokuz Eylül University were included in this retrospective cross-sectional study. Antibody levels against hepatitis A, hepatitis B, and rubella were routinely assessed both at the time of diagnosis and six months after completion of chemotherapy. However, measles, mumps, and varicella antibody levels were evaluated just six months after the treatment.
Results: Seventy-eight children who completed chemotherapy for ALL were recruited. All participants had nonprotective antibody levels for at least one of the diseases. The highest seropositivity rate was found for hepatitis A (55.1%) and the lowest for measles (17.9%) after

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chemotherapy. Overall, 50.7%, 30.6%, and 45.7% of the patients significantly lost their humoral immunity against hepatitis B, hepatitis A, and rubella, respectively. Patients in the higher-risk group for ALL had a lower seropositivity rate than the other risk group patients. There were statistically significant relations between the protective antibody rates of hepatitis A and varicella and the age of the patients. Except for the hepatitis A vaccination, pre-chemotherapy vaccination did not affect post-chemotherapy serology. On the other hand, all children with a history of varicella before the diagnosis showed immunity after chemotherapy.
Conclusion: All patients, including those previously fully vaccinated, are at great risk of infection due to the decrease in protective antibody levels after chemotherapy. There is a need for routine post-chemotherapy serologic testing and re-vaccination based on the results obtained.
Key words: Immunoglobulins; Infection; Pediatric Leukemia; The Humoral Immune Response

Öz
Amaç: Akut lenfoblastik lösemi (ALL) tanılı çocukların hayatta kalma oranları yıllar içinde artmış olsa da enfeksiyonlar önemli bir morbidite ve mortalite nedeni olmaya devam etmektedir. Uygulanan kemoterapinin, aşıyla önlenebilir hastalıklara karşı koruyucu antikorların kaybı da dâhil olmak üzere bir dizi zararlı yan etkisi vardır. Bu çalışmanın amacı pediatrik ALL olgularının yoğun kemoterapi öncesi ve sonrası serolojik durumlarını değerlendirmektir.
Gereç ve Yöntemler: Bu retrospektif kesitsel çalışmaya Dokuz Eylül Üniversitesi'nde ALL tanısıyla tedavi ve takip edilen çocuklar dahil edilmiştir. Hepatit A, hepatit B ve kızamıkçık antikor düzeyleri hem tanı anında hem de kemoterapinin tamamlanmasından altı ay sonra rutin olarak değerlendirilmiştir. Ancak, kızamık, kabakulak ve suçiçeği antikor düzeyleri sadece tedaviden altı ay sonra değerlendirilmiştir.
Bulgular: ALL kemoterapisini tamamlamış yetmiş sekiz çocuk çalışmaya alınmıştır. Çalışmaya alınan çocukların tamamı en az bir hastalığa karşı koruyucu olmayan antikor seviyelerine sahipti. Kemoterapi sonrasında en yüksek seropozitivite hepatit A'ya (%55,1) karşı iken, en düşük oran kızamığa (%17,9) karşı bulunmuştu. Genel olarak, hastalar kemoterapi sonrası hepatit B, hepatit A ve kızamıkçığa karşı humoral bağışıklıklarını anlamlı şekilde kaybetmişti (sırasıyla %50,7, %30,6 ve %45,7). ALL için yüksek risk grubundaki hastalarda seropozitiflik oranı diğer risk grubundaki hastalara göre daha düşüktü. Hepatit A ve suçiçeği koruyucu antikor oranları ile hastaların yaşları arasında istatistiksel olarak anlamlı bir ilişki vardı. Hepatit A aşısı dışında, kemoterapi öncesi aşılama kemoterapi sonrası serolojiyi etkilememiştir. Öte yandan, tanıdan önce suçiçeği öyküsü olan tüm çocuklar kemoterapi sonrasında da suçiçeğine karşı koruyucu antikor düzeylerine sahipti.
Sonuç: Daha önce tamamen aşılanmış olanlar da dâhil olmak üzere tüm hastalar, kemoterapi sonrası koruyucu antikor seviyelerindeki düşüş nedeniyle enfeksiyon açısından büyük risk altındadır. Kemoterapi sonrası rutin serolojik testlere ve tekrar aşılamaya ihtiyaç olduğunu düşünmekteyiz.
Anahtar Sözcükler: İmmünoglobulinler; Enfeksiyon; Pediatrik Lösemi; Hümoral Bağışıklık Yanıtı

Introduction
Acute lymphoblastic leukemia (ALL) is the most common malignancy in children, accounting for one-third of all childhood cancers [1]. Over the last decades, outcomes for pediatric ALL have improved dramatically. The widespread adoption of standardized treatment protocols improved clinical outcomes while reducing adverse events [2-4]. On the other hand,

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underlying malignant disease and intensive chemotherapy can cause long-lasting immunosuppression. The immune response may be impaired for 6 months, affecting both new and previously encountered antigens. As a result, patients may become more vulnerable to infections due to the decrease or disappearance of antibodies provided by vaccination [5,6]. The mechanisms of immune recovery after chemotherapy are not completely understood. However, a sufficient immune reconstruction is typically established within 6–12 months after treatment, and the re-vaccination program can produce adequate antibody levels for life-threatening vaccine-preventable infectious diseases (VPID) [7,8]. The Infectious Diseases Society of America (IDSA) guidelines recommend routine revaccination with a single dose of each vaccine [7]. Similarly, European Conference on Infections in Leukemia recommended a booster dose of all vaccines after the end of chemotherapy [9]. Further research may be required to determine whether revaccination is necessary and, if so, the optimal timing. The optimal vaccination strategy for ALL patients after chemotherapy remains uncertain. Only a limited number of studies have investigated the factors influencing the immunologic status of these patients. In addition, these studies should be performed regularly in countries with unique and constantly changing childhood infectious disease epidemiologies. Therefore, our study aimed to evaluate the changes in humoral immunity against some vaccine-preventable diseases in pediatric ALL patients before and after treatment and to identify the factors influencing seronegative patients for these diseases.

Materials and Methods

This retrospective cross-sectional study was conducted at the Dokuz Eylül University Children's Hospital. Patients diagnosed with ALL and followed up at the Pediatric Hematology Department between March 2016 and January 2024 were reviewed. Patients whose therapy was completed at least six months ago and who applied for a re-vaccination visit at the Social Pediatrics clinic during the study period were included in the study. Medical records were reviewed, and demographic and clinical characteristics (ALL type and risk group, date of onset, end of chemotherapy, pre- and posttreatment antibody levels, history of VPID) were collected. Children who relapsed or underwent hematopoietic stem cell transplant were excluded.

Data on past vaccinations were obtained from their vaccination cards. If the vaccination cards were not available, the information was collected through a standardized questionnaire. In that situation, if they could not remember any of their vaccination history, they were excluded from this analysis. In Türkiye, all children born after 1992 have been vaccinated against hepatitis B. Since 2007, children have routinely received the Measles, Mumps, Rubella (MMR) vaccination in two doses at 1 and 4 years of age. Before 2007, the measles vaccine was given at nine months of age. Since 2020, due to the risk of measles epidemic, additional measles vaccine has been given at nine months of age. Hepatitis A and varicella vaccines were added to the national program in 2012 and 2013, respectively. The hepatitis A vaccine is given in two doses (at 18 and 24 months), while the varicella vaccine is given in a single dose (at 12 months) [10].

All patients were classified into risk groups (Standard risk (SR), Intermediate risk (IR), and High risk (HR)) and treated with the ALL-Berlin–Frankfurt–Münster (ALL-BFM) 2000 protocol [11,12]. Patients who completed maintenance therapy six months ago were vaccinated according to the IDSA guidelines after being serologically tested in the Social Pediatrics Department [7]. In our center, inactive vaccines start to be administered in the sixth month after chemotherapy, and live vaccines in the 12th month after chemotherapy. Serologic testing for hepatitis A (HAV), hepatitis B (HBV), and rubella was routinely performed both at the time of diagnosis and six months after completion of chemotherapy. However, antibody levels against measles, mumps and varicella were assessed six months after completion of chemotherapy. The Enzyme-linked Immunosorbent Assay (ELISA)

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method was used to measure IgG antibodies for measles, mumps, rubella, varicella, HAV and HBV (anti-HBs). The serologic status of patients was evaluated according to the laboratory test manufacturer's references. Clear positive antibody results defined protective humoral immunity, whereas equivocal and negative test results were defined as nonprotective immunity.

Ethics

The study was approved by the Dokuz Eylül University Ethics Committee (approval number: 2024/06-12) and performed according to the principles of the Declaration of Helsinki. Informed written consent was not obtained because of the retrospective nature of the study.

Statistical Analysis

Statistical analyses were conducted with SPSS (version 21.0 for Windows; SPSS, Chicago, IL, USA). The normality of data distribution was checked using the Kolmogrov-Smirnov test. Categorical variables were compared by the chi-square test or Fisher's exact test, as appropriate. Willcoxon test was used to changing seronegative in vaccine-prevented diseases after treatment. For comparing means, data were analyzed with Student's t test in values with normal distribution and Mann-Whitney U test in cases with skewed data. The results were presented as mean ± standard deviation and/or median. A p-value <0.05 was considered significant.

Results

After screening using the inclusion and exclusion criteria, 81 children were included in the present study. However, 3 children were excluded because one child relapsed and underwent hematopoietic stem cell transplantation and two could not provide a clear vaccination record. Therefore, seventy-eight patients (35 males, 43 females) participated in this study. The mean age at diagnosis was 62.0 ± 45.1 and the median age was 47 months (range 11–203). There were 15 (19.2%) patients in the SR group, 55 (70.5%) in the IR group, and 8 (10.3%) in the HR group (Table 1). Patients were vaccinated according to the then-current Turkish National Immunization Program. At the time of ALL diagnosis, all the patients were fully vaccinated with their vaccination schedule. On detailed analysis, twenty-seven (34.6%) patients had received two doses, thirty-eight (48.7%) patients had received one dose of MMR vaccine, and thirty-four (43.6%) patients had received one dose of varicella vaccine (as recommended in the regular vaccination schedule of Türkiye). Eleven (14.1%) patients had received a single dose of measles vaccine and one patient had received neither measles nor MMR vaccine. Six (7.7%) patients had a history of varicella before the diagnosis of ALL.

A statistically significant decrease was observed in HBV, HAV, and Rubella seropositivity rates between the time of diagnosis and the sixth month after treatment ($p < 0.001$). Overall, 50.7%, 30.6%, and 45.7% of the patients lost their humoral immunity against hepatitis B, hepatitis A, and rubella, respectively (Table 2). The highest seropositivity rate was found for HAV (55.1%), and the lowest for measles (17.9%) after chemotherapy.

Upon evaluation of the immunization status of patients at the time of ALL diagnosis, it was observed that all patients vaccinated with hepatitis A were seropositive ($p < 0.001$). In contrast, only 90.9% of those vaccinated with rubella were seropositive ($p = 0.601$). Six months after chemotherapy, children who had received the HAV vaccine had a statistically higher rate of seropositivity ($p < 0.001$). However, no similar association was found between the MMR or varicella vaccines and seropositivity rates for measles, rubella, mumps, or varicella ($p > 0.05$). There was also no statistically significant association between vaccine dose (one or two doses of MMR vaccine) and seropositivity rates for measles, rubella, or mumps six months after chemotherapy ($p > 0.05$). Regarding varicella, we noted that among the six patients with a history of chickenpox before ALL diagnosis, all of them were seropositive after chemotherapy, and this difference was statistically significant ($P < 0.001$).

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There was no significant difference in sex, white blood cell counts at diagnosis, risk group, or immunophenotype criteria between seronegative and seropositive patients six months after the chemotherapy (Table 3). Although not statistically significant, the patients in the higher-risk group for ALL had a lower seropositivity rate than the other risk group patients. There were statistically significant differences between the protective antibody rates of hepatitis A and varicella and the patient's age (< 7 years vs. ≥ 7 years). When seropositive and seronegative cases against hepatitis A were compared, we found that ages of seropositive patients were significantly younger than those of seronegative cases (median 41 months versus 58 months, respectively. $p = 0.036$). On the other hand, seropositivity against varicella was statistically higher in older children (median 89 months versus 41 months, respectively. $p = 0.002$).

Discussion

A higher infection rate was observed in leukemia survivors compared to that of normal children, which has been identified as a significant cause of morbidity and mortality [13,14]. ALL patients, even those who have been previously vaccinated, are at a high risk of infection due to the decrease in protective antibody levels and inadequate response to specific infections after chemotherapy [3,4,9,13]. All participants in our study had nonprotective antibody levels to one or more of the antigens tested, despite being fully vaccinated, indicating susceptibility to VPID after chemotherapy. In previous studies, Anafy et al. [15] found that 96% of their patients did not have positive serology to at least one of the VPID, and Garonzi et al. [16] reported that 83% of patients had seronegativity for at least one VPID. The percentage of children with positive serology was the highest against hepatitis A (55.1%) and the lowest for measles (17.9%) in our study. In another study, 46% of patients were protected against HAV, 40% against varicella, 39% against measles, and 34% against HBV after chemotherapy [15]. Aytaç et al. [14] demonstrated that after completion of chemotherapy, the majority of cases had antibody levels lower than protective values for measles (58.4%); however, these rates were 47.3% for mumps and 26.3% for rubella. The interesting finding in the results was that although 67 patients were vaccinated against rubella, the number of anti-rubella IgG-positive patients was 70 at the time of diagnosis. Similarly, while the number of children with HAV vaccinations before diagnosis was 35, HAV seropositivity was found in 62 children. We thought this may have been due to an asymptomatic natural infection in the children, although these diseases were not found in their medical history.

Our study also revealed a statistically significant reduction in seroprotection rates for HBV, HAV, and rubella between the diagnosis of ALL and six months after the treatment ($p < 0.001$). A recent meta-analysis showed that the reduction of protective antibody titers measured 6–12 months after chemotherapy: it was about 50% for HBV, and 20 to 40% for measles, mumps, rubella [17]. Our low seroprotection levels for VPID were consistent with the literature. Several factors may explain the low levels of seroprotection observed after chemotherapy. First, the direct negative effect of chemotherapy on the immunity acquired by previous vaccinations before the diagnosis of ALL [18]. Second, there was a lack of regular and catch-up immunization practices. Most patients had received their primary vaccination series before chemotherapy, but none could receive their childhood or adolescent booster during ALL treatment.

It is noteworthy that only the HAV pre-chemotherapy vaccination demonstrated a statistically significant impact on post-chemotherapy seropositivity in our study. Conversely, the other pre-chemotherapy vaccinations (even the number of doses) did not exhibit the same effect. We speculated that the higher post-chemotherapy hepatitis A seropositivity seen in HAV-vaccinated children might be explained by the boosting effect of asymptomatic infections seen in those children. De la Fuente Garcia et al. [18] found that most children (81%) with a history of varicella before ALL diagnosis were seroprotected after chemotherapy ($p = 0.04$).

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In our study, all children with a history of varicella before ALL diagnosis showed immunity after chemotherapy. These findings indicate that natural infection may provide more durable protection than vaccination in this population. We can conclude that all patients, including those previously fully vaccinated, are at great risk of infection due to the decrease in protective antibody levels.

Some studies have found a negative correlation between a patient's age and the loss of protective antibody levels for VPID [8,14,19]. They suggested that this may be due to the developing B lymphocyte pool being more vulnerable in younger children during chemotherapy than in older children or to an incomplete national immunization program at younger ages [14-16]. However, other studies have found no association with age at diagnosis when analyzing risk factors for loss of immunity [15,16,20]. In our study, we found statistically significant differences only between HAV and varicella protective antibody levels and age at diagnosis. While 58.6% of children under seven years of age were vaccinated against HAV, this rate dropped to 5.0% in children aged seven years and older ($p < 0.001$). This decline in vaccination rates may be a contributing factor to the high HAV seropositivity observed in children under seven years of age. Additionally, it is known that older age may indicate previous varicella infection [16,21]. As in other studies, we did not find an association between sex and loss of immunity [14,15,19,20].

It has been shown that immune recovery is slower in the high-risk group of childhood ALL than in the standard or intermediate-risk groups [21]. On the other hand, many studies showed no significant difference between ALL risk groups and protective antibody levels [15,20,22-24]. Although it is not statistically significant, the percentage of seropositive patients six months after chemotherapy was lower in HR group patients compared to SR or IR group patients for all VPID in our study. Another study from Türkiye found no significant difference between ALL risk groups and protective antibody levels of VPID except varicella [8]. The observed outcomes may be attributed to the fact that the studies were conducted in small groups. Therefore, we recommend conducting more studies with a larger number of patients, including meta-analyses.

Our study has several limitations. First, except for HAV, HBV, and rubella, antibody levels to vaccine antigens were not measured before chemotherapy, so we cannot confirm that chemotherapy was the cause of low post-chemotherapy titers. However, all our patients were up-to-date on their vaccination schedule before their diagnosis, which is our strength. Second, we measured antibody titers only once after the chemotherapy (about six months afterward) but did not repeat to see if the immunity persisted over time. Other drawbacks include the small number of patients recruited at a single site and the absence of a control group.

Conclusion

The evaluation of long-term humoral immunity and vaccine-specific antibodies is complex due to various factors, such as the local epidemiology of infectious diseases, immunization recommendations, and social differences within communities. However, the findings of our retrospective study, together with those from the literature, suggest that chemotherapy may lead to a loss of humoral immunity in pediatric ALL patients, even if they were vaccinated. Our results underline the need for routine post-chemotherapy serologic testing and re-vaccination based on the results obtained. It's important to note that this study was not designed to determine the optimal timing for safe and effective vaccination in this population. Therefore, further large prospective multicenter studies are needed to determine the optimal timing for re-immunization.

Abbreviations: ALL: Acute lymphoblastic leukemia, ALL- BFM: ALL-Berlin-Frankfurt-Münster, ELISA: Enzyme-linked Immunosorbent Assay, HAV: Hepatitis A virus, HBV:

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Hepatitis B virus, HR: High risk, IDSA: The Infectious Diseases Society of America, IR: Intermediate risk, MMR: Measles mumps rubella, MRD: Minimal residual disease, SR: Standard risk, VPID: Vaccine preventable infectious diseases, WBC: White blood cell

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Table 1. Demographic features of patients who participated to study.	
Variable	Number (%)
Sex	
Male	35 (44.9)
Female	43 (55.1)
Age at diagnoses (month)	
Mean ± SD	62 ± 45.1
Median (range)	47 (11-203)
White blood cell counts at diagnosis (x10^9/L)	
Mean ± SD	22,7 ± 37,3
Median (range)	8.8 (1.2 - 228.4)
ALL risk group	
Standard-risk group	15 (19.2)
Intermediate-risk group	55 (70.5)
High-risk group	8 (10.3)
Immunophenotype	
Pre-B cell	69 (88.5)
T cell	9 (11.5)
Pretreatment vaccination status (vaccinated)	
Hepatitis B	78 (100.0)
Hepatitis A	35 (44.9)
Measles	77 (98.7)
Mumps	66 (84.6)
Rubella	67 (84.6)
Varicella	34 (43.6)

Table 2. Serologic characteristics of patients at the time of diagnosis and at the end of chemotherapy.			
	Rate of seropositivity		
Disease	**Diagnosis time n (%)**	**Six months after end of chemotherapy n (%)**	**P value**
Hepatitis B	65 (83.3)	32 (41.0)	**<0.001***
Hepatitis A	62 (79.5)	43 (55.1)	**<0.001***
Rubella	70 (89.7)	38 (48.7)	**<0.001***
Measles		14 (17.9)	
Mumps		15 (19.2)	
Varicella		21 (26.9)	
*p of significance if <0.05			

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Table 3. Comparison of Serologic Responses of ALL Patients According to Some Clinical and Laboratory Findings

	Sex			**Age at diagnosis**			**ALL risk group**				**WBC at diagnosis (x10^9/L)**		
	Male	Female	p	< 7 years	≥ 7 years	p	SR	IR	HR	p	< 50	≥ 50	p
Hepatitis B, n (%)													
Seronegative	18 (51.4)	28 (65.1)	0.322	36 (62.1)	10 (50.0)	0.495	8 (53.3)	31 (56.4)	7 (87.5)	0.248	38 (55.9)	8 (80.0)	0.184
Seropositive	17 (48.6)	15 (34.9)		22 (37.9)	10 (50.0)		7 (46.7)	24 (43.6)	1 (12.5)		30 (44.1)	2 (20.0)	
Hepatitis A, n (%)													
Seronegative	14 (40.0)	21 (48.8)	0.581	20 (34.5)	15 (75.0)	**0.004***	5 (33.3)	24 (43.6)	6 (75.0)	0.170	31 (45.6)	4 (40.0)	1.000
Seropositive	21 (60.0)	22 (51.2)		38 (65.5)	5 (25.0)		10 (66.7)	31 (56.4)	2 (25.0)		37 (54.4)	6 (60.0)	
Measles, n (%)													
Seronegative	30 (85.7)	34 (79.1)	0.643	48 (82.8)	16 (80.0)	0.746	11 (73.3)	46 (83.6)	7 (87.5)	0.635	56 (82.4)	8 (80.0)	1.000
Seropositive	5 (14.3)	9 (20.9)		10 (17.2)	4 (20.0)		4 (26.7)	9 (16.4)	1 (12.5)		12 (17.6)	2 (20.0)	
Rubella, n (%)													
Seronegative	15 (42.9)	25 (58.1)	0.265	28 (48.3)	12 (60.0)	0.519	6 (40.0)	29 (52.7)	5 (62.5)	0.549	34 (50.0)	6 (60.0)	0.738
Seropositive	20 (57.1)	18 (41.9)		30 (51.7)	8 (40.0)		9 (60.0)	26 (47.3)	3 (37.5)		34 (50.0)	4 (40.0)	
Mumps, n (%)													
Seronegative	30 (85.7)	33 (76.7)	0.477	46 (79.3)	17 (85.0)	0.747	11 (73.3)	45 (81.8)	7 (87.5)	0.734	55 (80.9)	8 (80.0)	1.000
Seropositive	5 (14.3)	10 (23.3)		12 (20.7)	3 (15.0)		4 (26.7)	10 (18.2)	1 (12.5)		13 (19.1)	2 (20.0)	
Varicella, n (%)													
Seronegative	23 (65.7)	34 (79.1)	0.286	49 (84.5)	8 (40.0)	**< 0.001***	11 (73.3)	40 (72.7)	6 (75.0)	0.994	49 (72.1)	8 (80.0)	0.721
Seropositive	12 (34.3)	9 (20.9)		9 (15.5)	12 (60.0)		4 (26.7)	15 (27.3)	2 (25.0)		19 (27.9)	2 (20.0)	

ALL: Acute lymphoblastic leukemia, HR: High risk, IR: Intermediate risk, SR: Standard risk, WBC: White blood cell
* P < 0.05

uncorrected proof