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 intensive chemotherapy.

Materials and Methods: Children treated and followed 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 at both the time of diagnosis and 6 months after completion of chemotherapy. Measles, mumps, and varicella antibody levels were evaluated at only 6 months after treatment.

Results: Seventy-eight children who completed chemotherapy for ALL were enrolled in the study. All participants had non-protective 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 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 lower seropositivity rates than patients of the other risk groups. There were statistically significant relationships between the protective antibody rates for hepatitis A and varicella and the ages of the patients. Except for hepatitis A vaccination, pre-chemotherapy vaccination did not affect post-chemotherapy serology. On the other hand, all children with a history of varicella before diagnosis showed immunity after chemotherapy.

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.

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Abstract

Conclusion: Patients with ALL, 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 serological testing and re-vaccination based on the results obtained.

Keywords: Immunoglobulins, Infection, Pediatric leukemia, Humoral immune response

Öz

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 [2,3,4]. However, the 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 re-vaccination programs can produce adequate antibody levels for life-threatening vaccine-preventable infectious diseases (VPIDs) [7,8]. The guidelines of the Infectious Diseases Society of America (IDSA) recommend routine re-vaccination with a single dose of each vaccine [7]. Similarly, the 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 re-vaccination 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 immunological status of these patients. Such research should be performed regularly in countries with unique and constantly changing childhood infectious disease epidemiologies. Therefore, the present 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 seronegativity 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 in the pediatric hematology department between March 2016 and January 2024 were reviewed. Patients whose therapy was completed at least 6 months previously and who applied for a re-vaccination visit at the social pediatrics clinic during the study period were included in the analysis. Medical records were reviewed and demographic and clinical characteristics (ALL type and risk group, date of onset, end of chemotherapy, pre- and post-treatment antibody levels, history of VPIDs) were collected. Children who relapsed or underwent hematopoietic stem cell transplantation were excluded.

Data on past vaccinations were obtained from the patients' vaccination cards. If vaccination cards were not available, the information was collected with a standardized questionnaire. In that case, if the parents could not remember any of the child's vaccination history, the child was excluded from that analysis. In Türkiye, all children born after 1992 have been vaccinated against hepatitis B. Since 2007, children have routinely received the measles, mumps, and rubella (MMR) vaccination in two doses at 1 and 4 years of age. Before 2007, the measles vaccine was given at 9 months of age. Since 2020, due to the risk of a measles epidemic, an additional measles vaccine has been given at 9 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 ALL 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 had completed maintenance therapy 6 months previously were vaccinated according to the IDSA guidelines after being serologically tested in the social pediatrics clinic [7]. In our center, inactive vaccines start to be administered in the sixth month after chemotherapy and live vaccines in the twelfth month after chemotherapy.

Serological testing for hepatitis A virus (HAV), hepatitis B virus (HBV), and rubella was routinely performed at both the time

of diagnosis and 6 months after completion of chemotherapy. However, antibody levels against measles, mumps, and varicella were only assessed 6 months after completion of chemotherapy. The enzyme-linked immunosorbent assay method was used to measure immunoglobulin (Ig) G antibodies for measles, mumps, rubella, varicella, HAV, and HBV (anti-HBs). The serological status of the patients was evaluated according to the laboratory test manufacturers' references. Clear positive antibody results defined protective humoral immunity, whereas equivocal and negative test results were defined as non-protective immunity.

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 IBM SPSS Statistics 21.0 for Windows (IBM Corp., Armonk, NY, USA). The normality of the data distribution was checked using the Kolmogorov-Smirnov test. Categorical variables were compared by chi-square test or Fisher's exact test as appropriate. The Wilcoxon test was used to evaluate seronegativity to vaccine-prevented diseases after treatment. For comparisons of mean values, data were analyzed with Student's t-test for values with normal distribution and with the Mann-Whitney U test in cases of skewed data. The results were presented as mean ± standard deviation and/or median. Values of $p<0.05$ were considered significant.

Results

After application of the inclusion and exclusion criteria, 81 children were included in the present study. However, 3 children were later excluded because one relapsed and underwent hematopoietic stem cell transplantation and two did not have clear vaccination records. Therefore, 78 patients (35 male, 43 female) were analyzed in this study. The mean age at diagnosis was 62.0±45.1 months and the median age was 47 (range: 11-203) months. 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 according to their vaccination schedules. Twenty-seven (34.6%) patients had received two doses and 38 (48.7%) patients had received one dose of the MMR vaccine, and 34 (43.6%) patients had received one dose of the varicella vaccine, as recommended in the regular vaccination schedule of Türkiye. Eleven (14.1%) patients had received a single dose of the measles vaccine and one patient had received neither the 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 HBV, HAV, and rubella, respectively (Table 2). The highest seropositivity rate after chemotherapy was found for HAV (55.1%) and the lowest for measles (17.9%).

Upon evaluation of the immunization status of the patients at the time of ALL diagnosis, it was observed that all patients vaccinated for HAV were seropositive ($p<0.001$). In contrast, only 90.9% of those vaccinated for rubella were seropositive ($p=0.601$). Six months after chemotherapy, the 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 vaccine 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 6 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

Table 1. Demographic characteristics of patients analyzed in this study.

Variable	Number (%)
Sex	
Male	35 (44.9)
Female	43 (55.1)
Age at diagnosis (months)	
Mean ± SD	62±45.1
Median (range)	47 (11-203)
White blood cell count 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)

SD: Standard deviation; ALL: acute lymphoblastic leukemia.

Table 2. Serological characteristics of patients at the time of diagnosis and at the end of chemotherapy.

	Rate of seropositivity		
Disease	**Time of diagnosis, n (%)**	**Six months after end of chemotherapy, n (%)**	**p**
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)	

*: Significant at p<0.05.

them were seropositive after chemotherapy, and this difference was statistically significant (p<0.001).

There was no significant difference in sex, white blood cell count at diagnosis, risk group, or immunophenotype criteria between seronegative and seropositive patients 6 months after chemotherapy (Table 3). Although not statistically significant, the patients in the HR group for ALL had a lower seropositivity rate than patients in the other risk groups. There were statistically significant differences between the protective antibody rates of HAV and varicella and the patient's age (<7 years versus ≥7 years). When seropositivity and seronegativity for HAV were compared, we found that the seropositive patients were significantly younger than the seronegative patients (median: 41 months versus 58 months, respectively; p=0.036). On the other hand, seropositivity for varicella was statistically significantly more common among older children (median: 89 months versus 41 months, respectively; p=0.002).

Discussion

Higher infection rates are observed in leukemia survivors compared to healthy 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 HR of infection due to the decrease in protective antibody levels and inadequate responses to specific infections after chemotherapy [3,4,9,13]. All participants in our study had non-protective antibody levels against one or more of the antigens tested despite being fully vaccinated, indicating susceptibility to VPIDs after chemotherapy. In previous studies, Anafy et al. [15] found that 96% of their patients did not have positive serology to at least one 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 highest for HAV (55.1%) and 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]. Aytac et al. [14] demonstrated that after completion of chemotherapy, the majority of patients had antibody levels lower than the protective values for measles (58.4%); however, that rate was 47.3% for mumps and 26.3% for rubella. An interesting finding in this study 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 vaccination before diagnosis was 35, HAV seropositivity was found in 62 children. This may have been due to an asymptomatic natural infection in the children although these diseases were not noted in their medical histories.

Our study also revealed a statistically significant reduction in seroprotection rates for HBV, HAV, and rubella between the diagnosis of ALL and 6 months after treatment (p<0.001). A recent meta-analysis showed that the reduction of protective antibody titers measured 6-12 months after chemotherapy was about 50% for HBV and 20% to 40% for MMR [17]. Our low seroprotection levels for VPIDs were consistent with the literature. Several factors may explain the low levels of seroprotection observed after chemotherapy. First, there is a direct negative effect of chemotherapy on the immunity acquired through previous vaccinations before the diagnosis of ALL [18]. Second, in this study, 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 childhood or adolescent boosters 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 considering the number of doses, did not exhibit the same effect. We speculated that the higher post-chemotherapy HAV seropositivity seen in HAV-vaccinated children might be explained by the boosting effect of asymptomatic infections seen in those children. de 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). In our study, all children with a history of varicella before ALL diagnosis showed immunity

Table 3. Comparison of serological responses of 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)	

*: p<0.05. ALL: Acute lymphoblastic leukemia; SR: standard risk; IR: intermediate risk; HR: high risk; WBC: white blood cell count.

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 VPIDs [8,14,19]. It was 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 [14,15,16]. 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 7 years of age were vaccinated against HAV, this rate dropped to 5.0% in children aged 7 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 7 years of age. Additionally, older age may have had 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 HR group of pediatric ALL patients than in the SR or IR groups [21]. On the other hand, many studies showed no significant difference between ALL risk groups and protective antibody levels [15,20,22,23,24]. Although the finding was not statistically significant, the percentage of seropositive patients 6 months after chemotherapy was lower in the HR group of patients compared to the SR or IR groups for all VPIDs in our study. Another study from Türkiye found no significant difference between ALL risk groups and protective antibody levels against VPIDs other than varicella [8]. The observed outcomes may be attributed to the fact that these studies were conducted with small groups. Therefore, we recommend conducting more studies with larger numbers of patients, including meta-analyses.

Study Limitations

Our study has several limitations. First, except for HAV, HBV, and rubella, antibody levels to vaccine antigens were not measured before chemotherapy, and so we cannot confirm that chemotherapy was the cause of low post-chemotherapy titers. However, all of our patients were up-to-date on their vaccination schedules before diagnosis, which is a strength of this study. Second, we measured antibody titers only once after chemotherapy, at about 6 months afterwards, but did not repeat those measurements to see if the immunity persisted over time. Other limitations 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 serological testing and re-vaccination based on the results obtained. It is 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.

Ethics

Ethics Committee Approval: 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 Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: T.İ., Ö.T.G., Ş.Y., H.Ö., A.A.; Concept: T.İ., Ö.T.G., Ş.Y., H.Ö., A.A.; Design: T.İ., Ö.T.G., G.T.; Data Collection or Processing: T.İ., Ö.T.G., G.T.; Analysis or Interpretation: T.İ., Ö.T.G., Ş.Y., H.Ö.; Literature Search: T.İ., G.T.; Writing: T.İ., Ö.T.G.

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