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Original Article

Serological Changes against Hepatitis B Surface Antigen in Children and Adolescents Receiving Chemotherapy for Acute Leukemia

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Abstract. ***Background:*** **Vaccination for hepatitis B virus (HBV) after chemotherapy among pediatric patients with acute Leukemia is still a debated issue. We investigated HBV immunity before and after chemotherapy and assessed immune response to re-vaccination after chemotherapy.**
Methods**: We retrospectively analyzed data of children and adolescents aged <19 years requested for vaccination after chemotherapy for acute leukemia to evaluate hepatitis B surface antibody (HBsAb) status before and after chemotherapy and to identify factors related to HBsAb positivity after chemotherapy.**
Results**: Of 89 enrolled patients, 61 (68.5%) with acute leukemia were HBsAb positive before chemotherapy. Of these 61 patients, 48 (78.7%) seroconverted to HBsAb negative status after chemotherapy; there were 76 (85.4%) HBsAb negative patients after chemotherapy. HBsAb positive patients when compared to HBsAb negative patients after chemotherapy had a significantly higher HBsAb positive rate (100.0% vs. 63.2%, *p*=0.008) before chemotherapy. Following HBsAb testing after one dose of the HBV vaccination, 33 (43.4%) of the 76 HBsAb negative patients seroconverted to an HBsAb positive status. HBsAb positive patients after a single dose of HBV vaccination had a significantly higher HBsAb positive rate at the time of diagnosis compared to HBsAb negative patients (84.8% vs. 48.8%, *p*=0.001).**
Conclusions**: Based on these results, HBV re-vaccination after chemotherapy is recommended for all children and adolescents with acute leukemia. In addition, further investigation is required to improve the immunogenicity of HBV re-vaccination.**

Keywords: Chemotherapy; Hepatitis B vaccine; Hepatitis B virus; Leukemia; Child.

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Introduction. Given higher survival rates in patients with acute leukemia due to advancements in chemotherapy technologies and conservative treatment for cancer patients,[1] it has become more important to prevent long-term complications after treatment. In particular, pediatric cancer patients have a longer survival period after treatment than adult patients, and they are more likely to be affected by vaccine-

preventable diseases (VPDs) during this period. Therefore, it is necessary to establish a vaccination policy for pediatric cancer patient survivors. Hepatitis B virus (HBV) infection is a well-known VPD. The worldwide prevalence of HBV infection significantly decreased after HBV vaccination during infancy was introduced.[2]

Even in low HBV infection endemic areas, there is a need to focus on prevention of HBV infection after anti-cancer treatment as well as prevention and treatment of reactivation of a previous HBV infection caused by immune-compromised conditions or *de novo* HBV infection during chemotherapy for acute leukemia.[3] The 2013 Guideline for Vaccination of the Immunocompromised Host by the Infectious Diseases Society of America states that all patients, who received hematopoietic cell transplantations (HCTs), are recommended to have HBV vaccination after transplantation.[3] However, not all patients who underwent chemotherapy for acute leukemia are advised to undergo HBV vaccination after chemotherapy, except in certain cases based on age and risk factors.[3] One previous study reported that the positive rate of hepatitis B surface antibody (HBsAb) remained high after chemotherapy for pediatric acute leukemia; thus, it was recommended that such patients should continue the standard vaccination schedule.[4] In contrast, other studies have reported that universal HBV vaccination was required due to a significantly reduced HBsAb positive rate after chemotherapy for acute leukemia.[5-7] Additionally, a recent vaccination guideline for patients with hematological malignancies of the 2017 European Conference on Infections in Leukaemia (ECIL7) supports this universal vaccination strategy.[8]

The subjects in the present study were pediatric patients with acute leukemia from Korea, a low intermediate HBV infection endemic area where almost all children and adolescents have acquired immunity from vaccination during infancy. To facilitate the development of an HBV vaccination policy after chemotherapy for children and adolescents treated with chemotherapy only, we evaluated the HBsAb positive rate before and after treatment for acute leukemia. We also evaluated the immunogenicity of HBV vaccine after chemotherapy.

Patients and Methods.

Subjects. Patients included in this study were aged <19 years at the time of leukemia diagnosis, received chemotherapy for acute leukemia in the Department of Pediatrics at Seoul St. Mary's Hospital, The Catholic University of Korea, and were referred to the division of Pediatric Infection Diseases between January 2015 and June 2018 for vaccination after chemotherapy. Of the 187 referred patients, 64 who had received HCTs were excluded. From the remaining 123 patients, treated with chemotherapy only, we excluded 33 who did not have an HBsAb test at the time of diagnosis with acute leukemia, and one who received a qualitative radioimmunoassay (RIA) test for HBsAb instead of a quantitative enzyme-linked immunosorbent assay (ELISA). Retrospective analysis of the medical records for the remaining 89 patients was performed. The present study was performed after obtaining approval from the Institutional Review Board of Seoul St. Mary's Hospital (Approval number: KC18RESI0503).

Data collection and definitions. Demographic data, including sex and age, were gathered at the diagnosis of leukemia. Clinical data, including type of underlying acute leukemia and its treatment results, the risk group of acute lymphoblastic leukemia (ALL), time intervals between completion of chemotherapy and HBsAb testing, and between completion of chemotherapy and HBV vaccination, HBsAb titers at the time of acute leukemia diagnosis and after completing chemotherapy, and the complete blood cell count at the time of the HBsAb testing, were investigated. Furthermore, HBsAb titers after HBV vaccination were also investigated in patients who received HBV vaccination after chemotherapy. HBsAb tests were performed using a commercial quantitative ELISA kit (Elecsys® Anti-HBs, Roche Diagnostics GmBH, Mannheim, Germany); titers were summarized as follows: titers <2 IU/L, corresponding to the threshold of the test, were categorized as 1 IU/L and those >1,000 IU/L were categorized as 1,000 IU/L. Positive and negative antibodies were defined as HBsAb levels of ≥10 IU/L and <10 IU/L, respectively. Patients testing negative for HBsAb after chemotherapy received one dose of HBV vaccine (Hepavax-Gene® TF, Janssen Korea Ltd., Seoul, Korea) at a dose of 0.5 mL (10 μg of hepatitis B surface antigen [HBsAg]) for patients aged <11 years, and 1.0 mL (20 μg of HBsAg) for those aged ≥11 years. After at least 4 weeks post-vaccination, the HBsAb test was again performed. HBsAb negative patients whose HBsAb level increased to ≥10 IU/L after HBV vaccination were considered to have an anamnestic response. For patients still negative for HBsAb after one dose of HBV vaccine, a second and third dose were administered at least 1 month and 6 months after the first HBV vaccination, respectively.

Statistical analysis. The subjects were divided into HBsAb negative and positive patients based on their HBsAb titer after chemotherapy. Demographic and clinical data were compared between these two patient groups. Based on the HBsAb retest results determined after one dose of HBV vaccine in patients who received an HBV vaccination after chemotherapy, patients were divided into those with and without an anamnestic response, and then the two groups were

compared. For comparison of continuous data and categorical data between the patient groups, Mann-Whitney U and Fisher's exact tests were applied, respectively. The SPSS 21 program (IBM Corporation, Armonk, NY, USA) was used for statistical analyses, and statistical significance was defined as a *p*-value <0.05.

Results. The 89 study subjects included 58 (65.2%) males and 31 (34.8%) females with a median age of 8 years (range, 1-18 years). At baseline, there were 79 (88.8%) patients with ALL and 10 (11.2%) with acute myeloid leukemia (AML); all were at their first complete remission state. At the time of their diagnosis with acute leukemia, 61 (68.5%) patients were HBsAb positive (**Figure 1**); their median HBsAb titer was 67.15 IU/L (range, 11.02-1,000.00 IU/L). HBsAb positivity at the time of leukemia diagnosis was not associated with sex or type of underlying leukemia. However, significantly more patients aged <7 years were HBsAb positive compared to those and ≥7 years old (86.4% vs 62.7%, *p*=0.038) at the time of diagnosis.

Comparison between HBsAb positive and negative patients after chemotherapy. HBsAb testing was performed at a median of 3 months (range, 0-14 months) after completing chemotherapy. Two (2.2%) patients had received 1 g/kg of intravenous immunoglobulin 7 months before an HBsAb test. Regarding the 61 patients who were HBsAb positive at the time of leukemia diagnosis, 48 (78.7%) seroconverted to HBsAb negative after chemotherapy (**Figure 1**). For the remaining 13 (21.3%) patients who remained HBsAb positive after chemotherapy, the median HBsAb titer of 40.91 IU/L (range, 11.48-256.70 IU/L) was significantly lower than the 169.20 IU/L (range, 16.30-1,000 IU/L) reported at the time of their leukemia diagnosis (*p*=0.003). This median titer for these 13 patients at the time of leukemia diagnosis was significantly higher than the HBsAb titer

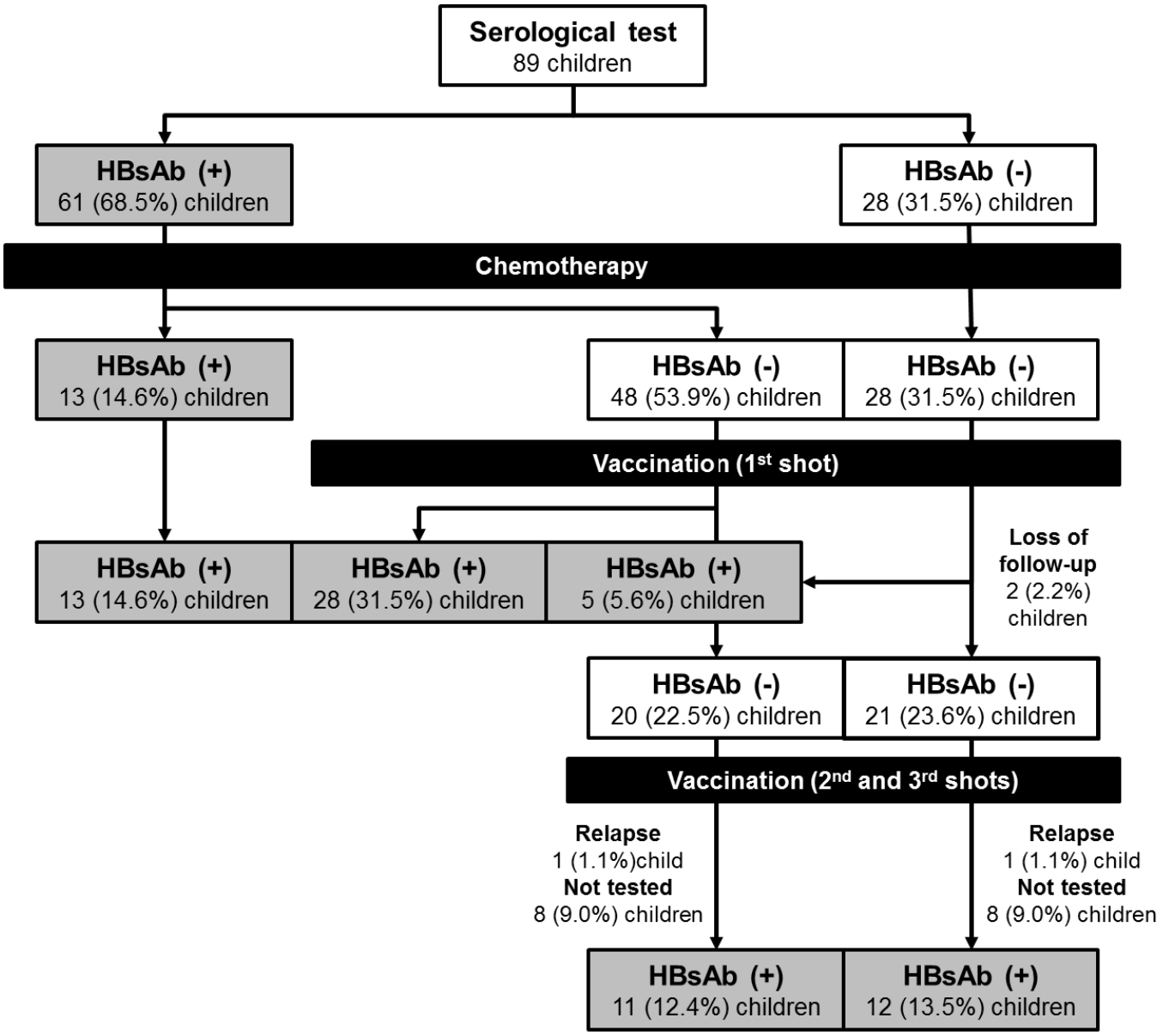

Figure 1. Summary of the study results.

determined at the time of leukemia diagnosis for the other 48 patients who seroconverted to negative after chemotherapy; the median was 53.57 IU/L (range, 11.02-819.00 IU/L, p=0.021). Only 30.6% (11/36) and 32.0% (8/25) of patients with an HBsAb titer of ≥50.00 IU/L and ≥100.00 IU/L before chemotherapy, respectively, remained HBsAb positive after chemotherapy. Compared to patients who were HBsAb negative after chemotherapy, more HBsAb positive patients had AML as an underlying disease (p<0.001) and were HBsAb positive at the time of leukemia diagnosis (p=0.008, **Table 1**). The risk group of ALL was not significantly associated with HBsAb positivity after chemotherapy. Younger age significantly correlated with HBsAb positivity at the time of diagnosis, but this correlation was not observed following chemotherapy. White blood cell, neutrophil and lymphocyte counts determined on the day of HBsAb testing were not significantly different between the two patient groups (data not shown).

Anamnestic response to the additional HBV vaccination after chemotherapy. All 76 patients who were HBsAb negative after chemotherapy received one dose of HBV vaccine at a median of 7 months (range, 3-18 months) after completing chemotherapy; of these, 74 were subjected to an antibody test at least 4 weeks after vaccination. Of these 74 patients, 33 (44.6%) seroconverted to HBsAb positive (**Figure 1, Table 2**), with a median titer of 45.72 IU/L (range, 10.27-1,000 IU/L). In comparison to the 41 patients who remained HBsAb negative after vaccination, the 33 seropositive patients were significantly more likely to be HBsAb positive (p=0.001, **Table 2**) and to have a higher HBsAb titer (median 8.22 IU/L vs 54.05 IU/L, p<0.001) at the time of leukemia diagnosis. White blood cell, neutrophil and lymphocyte counts determined on the day of first HBsAb test after chemotherapy were not significantly associated with anamnestic response to HBV vaccination after chemotherapy (data not shown). Of the 41 HBsAb negative patients, after one dose of HBV vaccination, 40 (excluding one patient with ALL relapse) received a second HBV vaccination, and 36 received a third vaccination (excluding one patient with ALL relapse after the second vaccination, one patient who was lost to follow-up after the second vaccination, and two who dropped out for unknown reasons). Regarding the 36 patients who received the third vaccination, 23 who had an antibody test performed after vaccination seroconverted to HBsAb positive, with a median HBsAb titer of 1,000 IU/L (range, 40.69-1,000 IU/L).

Table 1. Serological status against hepatitis B surface antigen after chemotherapy.

Factor	HBsAb negative (N=76)	HBsAb positive (N=13)	*p*- value
Sex, male	49 (64.5)	9 (69.2)	1.000
Age on leukemia diagnosis, yr, median (range)	6 (1-15)	5 (0-15)	0.744
Type of underlying leukemia			
Acute lymphoblastic leukemia	72 (94.7)	7 (53.8)	
Low risk	20 (27.8)	3 (42.9)	
Standard risk	19 (26.4)	3 (42.9)	<0.001
High risk	24 (33.3)	1 (14.3)	
Very high risk	9 (12.5)	0 (0.0)	
Acute myeloid leukemia	4 (5.3)	6 (46.2)	
HBsAb positivity on diagnosis of leukemia	48 (63.2)	13 (100.0)	0.008
Months from the completion of chemotherapy to HBsAb test, median (range)	3 (0-14)	3 (1-7)	0.641

HBsAb=Hepatitis B virus surface antibody.

Table 2. Serological status against hepatitis B surface antigen after one dose of hepatitis B virus vaccine.

Factor	HBsAb negative (N=41)	HBsAb positive (N=33)	*p*-value
Sex, male	25 (61.0)	22 (66.7)	0.613
Age on leukemia diagnosis, yr, median (range)	6 (1-15)	4 (2-15)	0.097
Type of underlying leukemia			
Acute lymphoblastic leukemia	37 (90.2)	33 (100.0)	
Low risk	7 (18.9)	13 (39.4)	
Standard risk	10 (27.0)	8 (24.2)	0.124
High risk	14 (37.8)	9 (27.3)	
Very high risk	6 (16.2)	3 (9.1)	
Acute myeloid leukemia	4 (9.8)	0 (0.0)	
HBsAb positivity on diagnosis of leukemia	20 (48.8)	28 (84.8)	0.001
Months from the completion of chemotherapy to vaccination, median (range)	7 (3-16)	6 (3-18)	0.562

HBsAb=Hepatitis B virus surface antibody.

Discussion. This study investigated HBV immunity before and after chemotherapy for acute leukemia and immune response to re-vaccination after chemotherapy. We found that 68.5% of children and adolescents who were diagnosed with acute leukemia were HBsAb positive at leukemia diagnosis. Of these HBsAb positive patients, 78.7% seroconverted to HBsAb negative after chemotherapy. As a result, 85.4% of all patients were HBsAb negative after chemotherapy. Of these patients, 44.6% seroconverted to HBsAb positive after a single HBV vaccination. Hence, 51.7% of all patients were HBsAb positive after one dose (Figure 1). All patients, who were subjected to testing after a third dose, exhibited seroconversion to an HBsAb positive status.

Although the HBV vaccination history could not be determined for all patients in the present study, 80.9% of the enrolled patients have received their three doses of vaccination during infancy; a rate that was determined based on their vaccination records. Furthermore, since mandatory HBV vaccination (thrice at birth and then at 1 and 6 months after birth) was incorporated into the National Immunization Program of Korea in 1995 with a maintenance of an HBV vaccination rate >93% after the 2000s,[9] almost all study subjects should have acquired HBsAb from HBV vaccination during infancy. Although the majority (95%) of healthy infants were HBsAb positive after three doses of primary HBV vaccination,[2] antibody titer and seroprevalence decreased over time, resulting in a 50-60% HBsAb positivity rate among children aged 6-8 years.[10-12] The HBsAb positive rate of the children enrolled in the present study (with a median age of 6 years) was similar to that of healthy children at 68.5%. HBsAb seroprevalence in healthy Korean children has been found to decrease by 17.0% from the age of six to eight,[10] whereas, the rate of seroconversion to HBsAb negative status of the patients enrolled in the present study was 78.7% during approximately 3 years of chemotherapy. This seroconversion rate was higher than the previously reported rates of 27.4-53.8% in pediatric patients receiving chemotherapy for hematological malignancies.[7,13,14] We speculate that the seroconversion rate could have been affected by differences in either intensity of chemotherapy among patients, antibody test methods, or the sensitivity and specificity of the ELISA kit used. Overall HBsAb positive rate after chemotherapy for hematological malignancy including acute leukemia ranges from 14.0-80.6% in studies, including this one.[4-7,13-16] However, all studies, except the one that showed the 80.6% positive rate, were below a 50% positive rate. Therefore, there is a need for universal HBV vaccination policy for patients with acute leukemia after chemotherapy rather than vaccination based on HBsAb test results, reconfirming the recent ECIL7 guideline for vaccination in patients with hematological malignancies.[8] HBsAb positivity in patients with acute leukemia after chemotherapy exhibited no significant correlation with age, sex, underlying leukemia, or the intensity of chemotherapy.[5-7,14,16] In the present study, patients who were HBsAb positive after chemotherapy had a significantly higher HBsAb positive rate and a significantly higher HBsAb titer before chemotherapy compared to those who were HBsAb negative after chemotherapy. Although a similar result was reported in another study,[14] the other study reported no significant correlation in HBsAb positivity before and after chemotherapy.[16] In healthy children, those with a higher HBsAb titer after their primary HBV vaccination during infancy exhibited a higher anamnestic response rate to re-vaccination after several years.[17-19] As such a higher HBsAb titer before chemotherapy may be considered to be a contributing factor to HBsAb positivity after chemotherapy. However, with low rates of patients with either HBsAb ≥10 IU/L (21.5%) or ≥100 IU/L (33.3%) before chemotherapy remaining HBsAb positive after chemotherapy, the prediction of HBsAb positivity after chemotherapy based on HBsAb positivity before chemotherapy would have limited usefulness in real-world clinical settings.

In the present study, about half of the patients had an anamnestic response after their initial HBV vaccination after chemotherapy. This implied that the remaining 48.3% of patients were HBsAb negative despite a single HBV vaccination after chemotherapy. In previous studies, higher percentages (63.2-95.7%) of patients who were HBsAb negative after chemotherapy were found with an anamnestic response after HBV vaccination.[5,7,15] Almost all (92.9-100%) healthy adolescents who receive their three doses of primary HBV vaccine during infancy have an anamnestic response to HBV re-vaccination, even after 10-20 years.[20-22] However, as low as 47.9% of healthy adolescents show an anamnestic response to re-vaccination after 15 years of HBV vaccination in infancy.[23] Such low anamnestic responses occurred when all three doses of the primary vaccination were administered within 6 months of birth, or when a low-dose vaccine (2.5 or 5.0 μg of HBsAg) was used.[12] In Korea, a 10 μg HBsAg vaccine has been used for infants; however, the vaccination is performed thrice within their first 6 months of age. It is, in fact, impossible to alter the national primary vaccination schedule for patients with acute leukemia only; thus, it is necessary to identify adjustable factors after chemotherapy that can improve HBV vaccine immunogenicity. Accordingly, it makes sense to consider the appropriate time interval between completion of chemotherapy and HBV vaccination. Although restoration of B-cells can be achieved 3-6

months following completion of chemotherapy, it may take several years for the restoration of memory B-cell counts.[24] In the present study, HBsAb testing and HBV vaccination were performed at medians of 3 and 7 months after completion of chemotherapy, respectively. Considering that previous studies described a >90% HBsAb seroconversion rate with HBV vaccination at least 15 months after chemotherapy,[5,7] an improved anamnestic response through delayed vaccination after the full restoration of memory cells should be possible. Therefore, vaccination may need to be postponed in countries with a low prevalence of HBV infection until there is a full restoration of lymphocytes in number and functionality, and one dose of vaccine rather than three doses may be adequate after chemotherapy with this strategy. Follow-up studies are needed to determine the appropriate time of immunity restoration after chemotherapy, in order to allow for the acquisition of full vaccine immunity without morbidity from VPDs. In addition, the immunogenicity of HBV vaccines after chemotherapy may be enhanced by the use of new adjuvant vaccines, vaccines containing new antigens, or vaccines with increasing dose of antigens.[25]

The present study has some limitations. Since there was no screening for antibodies against the HBV core antigen, it was not possible to establish which patients were previously HBV-infected. Patient history of HBV vaccination before chemotherapy was also not determined for all of the enrolled patients. However, with the recent high HBV vaccination rate during infancy and decreasing HBV infection prevalence in Korea, most patients should receive HBV vaccination before chemotherapy; thus, only few children should be HBV-infected. The present study also excluded patients not screened for HBV serology at the time of diagnosis, or who had RIA test instead of ELISA. Therefore, unified test items, times, and methods are necessary from the time of diagnosis with acute leukemia for future studies to establish an accurate vaccination schedule after chemotherapy.

Conclusions. The present study was unable to identify the significant factors of HBsAb positivity after chemotherapy and seroconversion by HBV vaccination after chemotherapy. However, it is useful to know that all patients should receive HBV vaccination after chemotherapy for acute leukemia in regions where almost all children have acquired HBV immunity from vaccination during infancy, and there is a low prevalence of HBV infection, in accordance with the recent ECIL7 guideline. In addition, there should be on-going studies on the appropriate vaccination time after chemotherapy and improving the immunogenicity of vaccines in immunocompromised patients.

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