

# Assessment of hepatitis B immunization status after antineoplastic therapy in children with cancer

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**BACKGROUND AND OBJECTIVES:** Hepatitis B is a disease that is preventable with vaccination. Antibody levels after vaccination may be affected by suppression of the immune system due to cancer therapy. Children with cancer have a high risk of hepatitis B virus (HBV) infection. We aimed to assess the pretreatment immunization status against HBV infection and the rate of continuity of immunization after therapy in children with cancer.

**DESIGN AND SETTING:** Retrospective case review of patients treated from 2004 to 2008.

**PATIENTS AND METHODS:** We reviewed the medical records of patients treated in the departments of pediatric hematology and oncology and collected data on immunization history and hepatitis B serology. Anti-HBs antibody titers were compared before and after treatment.

**RESULTS:** This study included 159 (99 males, 60 females) children who had a serologic examination. Antineoplastic therapy had been given for acute leukemia (n=66), non-Hodgkin lymphoma (n=27), Hodgkin lymphoma (n=20), and solid tumors (n=46). Fifty-one patients had not been immunized against HBV prior to the therapy; HBV serology was negative in 49 of these patients and HBsAg was positive in 2 patients. Anti-HBs antibody positivity was present in 99 of 108 patients with an immunization history, whereas no vaccination response was present in 9 patients. The titer of anti-HBs antibody was decreased below the protection level in 33 (33%) patients with positive anti-HBs antibody, whereas the protection level was found to be maintained in 66 (67%) patients. The most significant decrease (63.6%) was observed in leukemia patients. Posttreatment HBsAg and HBV DNA positivity was detected in two of the patients with negative pretreatment serology, whereas no HBV infection developed in the group with positive anti-HBs antibody.

**CONCLUSIONS:** This study demonstrated the importance of routine childhood vaccination in reducing the risk of HBV infection in patients with cancer.

Intensive therapy performed on patients with cancer suppresses the immune system and makes patients vulnerable to infections. Surgical intervention and transfusion of blood products also increase the risk for hepatitis B virus (HBV) infection. HBV infection is a vaccine-preventable disease. Although children who have not received routine childhood vaccination can be immunized during cancer therapy, vaccination may not be sufficient, as cancer therapy can cause loss of acquired vaccination status. The type of cancer and the therapy applied may influence the level of antibody titer.<sup>1</sup> In Turkey, HBV vaccination has been given in accordance with the government vaccination program since 1998.

In this study, we aimed to assess the pretreatment immunization status of patients against HBV infection, as well as the pretreatment and posttreatment antibody titers in immunized children.

## PATIENTS AND METHODS

The files of all patients treated in the Departments of Pediatric Oncology and Hematology (Sisli Etfal Education and Research Hospital Clinic of Pediatrics, Istanbul, Turkey) between January 2004 and December 2008 were retrospectively examined in terms of history of HBV vaccination and serology (HBsAg, anti-HBs antibody, and anti-HBc antibody). Hepatitis B

surface antigen (HBsAg), as well as the antibodies against HBsAg (anti-HBs) and HbC (anti-HbC), was examined using enzyme-linked immunosorbent assay methods. Antibody titers >10 mIU/mL were considered anti-HBs positive, and neither pretreatment nor posttreatment additional vaccination was applied. The pretreatment and posttreatment titers were compared; the effects of age, gender, antibody titer, and diagnosis on the level of antibody were evaluated in patients whose antibody titers decreased below the protection levels after the treatment. The prevalence of HBV infection among children with and without childhood vaccination was investigated. Institutional Review Board approval was not necessary since the study was retrospective.

**RESULTS**

The median age of the 159 patients was 5 years. Sixty were male and 99 were female. Sixty-six of these patients had been treated for leukemia, 27 for non-Hodgkin lymphoma, and 46 for advanced-stage solid tumors (Table 1). Fifty-one patients had not been immunized with hepatitis B vaccine prior to treatment; HBV serology was negative in 49 of these patients, whereas HBsAg was positive in 2 of them. Anti-HBs antibody was positive in 99 of 108 patients with a history of immunization, whereas HBV serology was found to be negative in 9 patients (Table 2). Anti-HBs antibody titer results of 33 (33%) patients decreased below the protection level after treatment, whereas the protection level of anti-HBs antibody titer was found to be maintained in 66 (67%) patients. It was determined that age, gender, and pretreatment antibody titers had no influence on the posttreatment antibody titers in patients

**Table 1.** Characteristics of the patients.

Characteristic	Number of patients
<b>Age</b>	
1-16 years (median, 5 years)	159
<b>Gender</b>	
Female	60
Male	99
<b>Primary disease</b>	
Acute lymphoblastic leukemia	66
Non-Hodgkin lymphoma	27
Hodgkin-lymphoma	20
Solid tumor	46

**Table 2.** Hepatitis B serology at the time of presentation at hospital.

Hepatitis B serology	Number of patients		
	Not immunized	Immunized	Total
HBsAg, anti-HBs, anti-HbC (-)	49	9	58
Anti-HBs (+)	0	99	99
HbsAg (+)	2	0	2

-, Negative; +, positive.

who had protective antibody levels prior to therapy. It was found that the antibody titers decreased below the protection levels in 63.6% of leukemia patients and in 15% of the other patients. In the regression analysis, having leukemia was found to be a predictive factor for the alteration of vaccination from positive responses to negative ones after treatment ( $P=.0001$ ; odds ratio, 9.8). Whereas posttreatment HBsAg and HBV DNA levels were found to be positive in two of the patients with negative pretreatment serology, no HBV infection was found to have developed in the group with positive anti-HBs (Table 3).

**DISCUSSION**

National immunization programs play a significant role in reducing the prevalence of HBV infection, which is a vaccine-preventable disease. In Turkey, HBV vaccination has been part of the routine childhood immunization schedule since 1998. In previous years, the prevalence of HBV infection among children was approximately 5% to 14% and was remarkably higher than the prevalence shown in other developed countries.<sup>2,3</sup> In studies performed during that period, the prevalence of HBV infection among children with cancer was reported to be as high as 20% to 65%.<sup>4,5</sup> In a previous study that we performed in our clinic that examined the years between 1995 and 1998, none of the patients had received childhood immunization, and the prevalence of HBV infection was 9.4% at the time of diagnosis, whereas it was 35.8% during or after their treatment.<sup>6</sup> Although none of the patients had been immunized before the diagnosis of cancer in our previous study, in our present study, 68% of the patients had received childhood immunization. In the present study, we found the seroprevalence of HBV during the initial screening to be 1.3% and HbsAg to be positive in only two patients. Because vaccination for hepatitis B was started routinely in 1998 as part of the national vaccination program and because the median age of patients

**Table 3.** Posttreatment hepatitis B serology of the patients with positive anti-HBs antibody.

Primary disease	Number of patients			
	Total	Anti-HBs (+)	Anti-HBs (-)	HBsAg (+)
Acute lymphoblastic leukemia	38	14	24	0
Non-Hodgkin lymphoma	16	13	3	0
Hodgkin lymphoma	10	6	4	0
Solid tumors	35	33	2	0

-, Negative; +, positive.

in our study group was 5 years, the patients in our study were vaccinated in the infantile period for hepatitis B. Despite the increase in the prevalence of pretreatment immunization in our hospital, which provides service to patients of very low socioeconomic status, 32% of the patients had not received childhood immunization and two of them had been treated for being HBV carriers. Surgical procedures and blood transfusions, in addition to immunosuppressive therapies, increase the risk of infection for hepatitis B during cancer chemotherapy.<sup>1</sup> Two patients who were HBsAg positive after chemotherapy were not vaccinated during the infantile period, and these patients had undergone surgical procedures during diagnosis and had multiple blood transfusions during chemotherapy. Although no problems related to HBV infection appeared in these patients during treatment, it is known that progression of HBV infection is serious in patients with cancer and the likelihood of becoming chronic is high; thus these considerations could lead to delay in cancer therapy.<sup>1,7,8</sup>

Immune system suppression may lead to a decrease in vaccine-mediated protection in patients who are immunized before therapy and have had a sufficient antibody titer.<sup>1</sup> Information about the effect of cancer therapy on vaccine-mediated immunization is not clear. There may be different factors that affect the antibody titers. Vaccine-mediated antibody titers of hepatitis B, measles, mumps, rubella, tetanus, and polio were determined to be negative by 46%, 25%, 26%, 24%, 14%, and 7%, respectively. It was found that the negativities of rubella, mumps, and tetanus antibodies were significantly influenced by age, whereas the negativity of measles antibody was significantly influenced by age and gender. The loss of antibody was more remarkable in younger patients and in girls.<sup>9</sup> In the present study, it was determined that age and gender had no effect on posttreatment antibody titers.

In a study performed on more homogenous types of cancers, it was determined that the decrease in vaccine-

mediated antibody titers for hepatitis B was highest in patients with sarcoma and that the posttreatment antibody titers decreased below the protection level in 64% of the patients.<sup>10</sup> In the present study, we investigated antibody titers in a heterogeneous group of patients, including those with leukemia, lymphoma, and solid tumors. The loss of antibody titers after therapy was determined to be the highest in patients with leukemia (63.6%), and diagnosis of the disease was the unique factor that statistically significantly affected the antibody titers. In a study performed on leukemia patients only, it was determined that the vaccine-mediated immunization had been lost by 56% of patients, which is in agreement with the present study.<sup>11</sup> It was demonstrated that the antibody response, particularly with vaccination during intensive therapy, was shorter in children with leukemia than in those with solid tumors.<sup>12</sup> An anti-HBs antibody titer above 10 IU/L is considered protective for hepatitis B infection.<sup>13</sup> There are studies suggesting that the antibody titer should be elevated in patients with immune deficiency.<sup>14</sup> In the present study, a protective anti-HBs antibody titer was considered to be above 10 IU/L, and vaccination was not repeated in such patients. No statistical difference in post-treatment antibody loss was found between those with anti-HBs antibody titer above 10 IU/L and those with anti-HBs antibody titer above 100 IU/L; HBV infection did not develop in either of these groups.

Memory cells exist years after the primary immunization and protection continues, even though the level of antibody titer decreases in time in healthy children immunized with hepatitis B vaccine.<sup>15</sup> There are no adequate data for immune-deficient patients, and generally repeated vaccination is recommended during and after therapy in patients whose antibody levels decrease below protection levels.<sup>1</sup> The prevalence of infection in immunized patients and the antibody titer may also be important in the evaluation of vaccine protection. In

a study performed in patients with leukemia, patients who had been immunized during therapy were compared with patients who had not been immunized in terms of the prevalence of HBV infection. A remarkable decrease was demonstrated in HBV infection in immunized patients, even though the antibody titer had not reached the protection level.<sup>16</sup> In the present study as well, despite the loss of antibody, we did not observe hepatitis B infection in any of the patients who received pretreatment immunization. HBV infection was observed in two patients in the group without immunization. Re-vaccination is recommended after chemotherapy, along with control of antibody levels, in all patients, especially in those with leukemias who have

been prescribed chemotherapy, as not enough studies show a continuation of protectivity when antibody loss has occurred after chemotherapy.<sup>1</sup>

In conclusion, it may be stated that one-third of our study patients were not immunized before treatment and that HBV infection was found to have developed in two patients during therapy. In those who had received routine immunization, protection continued in 67% despite immunosuppressive therapy. No HBV infection developed in the immunized group, including those with antibody titers that had decreased below the protection levels. It is thought that routine childhood immunization is important in reducing the risk for HBV infection in patients with cancer.

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