

Hepatitis B Vaccination in Children With Ongoing Cancer Treatment: A Safety and Efficacy Study of Super-Accelerated Vaccination Scheme

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What is already known on this topic?

- Turkey has been, and is still, a low-endemicity region for hepatitis B infections, and about 4% of the adult population in Turkey is hepatitis B surface antigen (HBsAg)-positive.
- Children with cancer have increased susceptibility to blood-borne infections due to immunodeficiency secondary to chemotherapy and frequent blood transfusions.

What this study adds on this topic?

- The hepatitis B virus (HBV) vaccination during induction chemotherapy of pediatric malignancies is safe, and effective antibody titers can be achieved.
- Sustained antibody responses to a 4-week accelerated scheme of HBV vaccination are possible in children with ongoing multi-drug, intensive cancer treatment, including high dose corticosteroids.

ABSTRACT

Objective: Children with cancer have an increased risk for hepatitis B virus (HBV) infections due to chemotherapy-induced secondary immunodeficiency and frequent blood transfusions. The aim of this study is to evaluate the efficacy and safety of hepatitis B vaccination during the intensive induction chemotherapy in children with cancer found to be seronegative for hepatitis B on admission.

Materials and Methods: Children newly diagnosed with cancer were evaluated for the presence of hepatitis B surface antigen (HBsAg) and antibody on admission. The children negative for both were included in the study. A super-accelerated vaccination scheme (3 booster doses at days 1-5, 8-12, and 28-33) was administered to these seronegative children concurrently with induction chemotherapy. Antibody response was checked 4-8 weeks after the last vaccination and 6 months after the end of the treatment.

Results: Eleven out of 122 children were seronegative for hepatitis B on admission (9%). Acute lymphoblastic leukemia, lymphoma, and solid tumors were diagnosed in 5, 4, and 2 children, respectively. Complete seroconversion was achieved in 4-8 weeks after the last vaccination with high titers of anti-HBs antibody, and all patients remained antibody-positive until 6 months after the completion of chemotherapy.

Conclusion: The risk of transfusion-related infections increases with a number of transfused products and donor exposures, and it is more significant for immunosuppressed children with hematologic and oncologic malignancies. Hepatitis B vaccination could safely be applied with brisk and sustained responses in this vulnerable population, based on the local epidemiological data.

Keywords: Cancer, chemotherapy, child, hepatitis B, booster vaccination

INTRODUCTION

The survival rates in pediatric cancers have significantly increased in recent decades due to improvement in diagnostics, risk stratification, and implementation of multimodal, intensive therapies.¹ However, the use of intensive chemotherapy protocols has also resulted in an immune dysfunction with increased susceptibility to infections in children with cancer.^{2,3,4,5} In addition to chemotherapy-induced immune suppression, frequent blood transfusions with multiple donor exposures poses an extra risk for blood-borne infections, such as hepatitis B or human immunodeficiency virus, in this population.⁶ Despite the use of nucleic acid technology in transfusion practices, the risk of transfusion-transmissible infections has not been completely resolved.^{7,8}

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Turkey has been, and still is, a low- to intermediate-endemicity region for HBV infections.⁹ A nationwide vaccination program has been present since 1998 in Turkey, but 4% of healthy adults and 1.54% of blood donors are HBsAg-positive and one-third of the population has been exposed to HBV infection.^{10,11}

In children with newly diagnosed cancer, vaccination with inactive or recombinant vaccines was recommended prior to initiation of chemotherapy whenever feasible.¹² In clinical practice, pediatric cancers are medical emergencies, and it is usually impossible to complete vaccination schemes before treatment. Although there are no standard guidelines for timing, vaccination against HBV during chemotherapy in children with cancers has been reported to be safe and effective in several reports.^{4,13} Alternative accelerated or super-accelerated schedules were reported to be feasible to get serologic response during chemotherapy or other conditions with altered immunity.^{14,15,16}

Based on this information, we aimed to evaluate the efficacy and safety of a rapid hepatitis B vaccination schedule in children with cancer found to have negative hepatitis B surface antibody (anti-HBs) titers at the time of diagnosis.

METHODS

Study Population and Clinical Data

Between January 2017 and December 2019, children (6 months to 18 years) with newly diagnosed malignancies were tested for HBV serology status on admission. HBsAg and anti-HBs were analyzed by enzyme-linked immunosorbent assay. Anti-HBs titers ≥ 10 IU/L and < 10 IU/L were defined as positive and negative, respectively. The children negative for both HBsAg and anti-HBs antibody were included in the study. Treatment details of the primary disease, complete blood counts, liver function tests, accompanying infections, disease status of the patients at the time of each vaccination, and local and systemic vaccine-related side effects were all noted. The study was approved by the Ethics Committee of Istanbul University (09.03.2021-115235), and a written informed consent was taken from legal guardians of all patients and children over 11 years of age upon inclusion in the study.

Vaccination Scheme and Response Evaluation

A super-accelerated vaccination scheme was designed based on the previous reports of significant acute and long-term protective antibody levels following multiple, double doses of vaccination during chemotherapy in children with cancer.^{14,15,16} Three doses (at days 0-5, 8-12, and 28-33) of booster recombinant HBV vaccines (Engerix-B, GlaxoSmithKline Pharmaceuticals Limited) were administered to children with cancer who were HBV seronegative (negative for HBsAg and anti-HBs Ab) at diagnosis.

The first dose of booster was administered in the first 5 days of initiation of chemotherapy, and the following doses were scheduled at days 8-12 and 28-33 of the first vaccination. Vaccination was cancelled in the presence of neutropenic fever, systemic infections, or significant thrombocytopenia (platelet count $< 30\,000/\text{mm}^3$). In case of severe thrombocytopenia, vaccination was postponed until after the transfusion of platelet concentrate.

To evaluate the response, anti-HBs antibody titer was measured 4-8 weeks after the last booster dose of vaccine and 6 months after the end of chemotherapy.

RESULTS

Clinical and Laboratory Features

One hundred twenty-two cases of newly diagnosed pediatric cancer were evaluated for HBV status. All were negative for HBsAg, and 11 children (9%) were also found to have negative anti-HBs titers during the study period. These 11 antibody-negative patients had previously completed the routine, 3-dose hepatitis B vaccination schedule in infancy, and they were accepted as vaccine nonresponders.

Median age at diagnosis was 6.7 years (range 2.2-17.8 years), and 8 of the patients were male. Acute lymphoblastic leukemia, lymphoma, and solid tumors were diagnosed in 5, 4, and 2 children, respectively. All vaccinations were performed concurrently with the induction chemotherapy. During the vaccination period, 8 patients were using corticosteroids as part of their chemotherapy protocols (prednisolone 60 mg/m²/day), and 1 patient with brain tumor for anti-edema effect (dexamethasone 10 mg/m²/day or 0.6 mg/kg/day). All but 1 patient received combination chemotherapy, and the patient with brain tumor was treated with single-agent chemotherapy and radiotherapy. None of the patients received intravenous immunoglobulins or monoclonal antibodies in the vaccination period. Lymphopenia and/or neutropenia ($<1500/\text{mm}^3$) were present in 6, 10, and 8 patients at the time of first, second, and third doses of vaccination, respectively. All vaccinations were performed in the defined time periods. No local or systemic vaccine-related side effects were recorded in the study population.

Response Evaluation

Anti-HBs antibody levels were checked 4-8 weeks after the last dose of vaccination and were positive (>10 IU/L) in all patients. The titer was above 100 IU/L in 8 patients with brisk response. The anti-HBs antibody titers were also measured 6 months after the completion of therapy and found to be positive (>10 IU/L) in all 11 cases, with levels of > 100 IU/L in 6 of them.

DISCUSSION

During cancer therapy, infections are among the major causes of morbidity and mortality in pediatric cancers. Protection of children with cancer from vaccine-preventable infections is an important goal.¹⁷ Hepatitis B infections are still a global health issue, and Turkey has a low to intermediate endemicity for HBV with a 4% HBsAg positivity in the adult population.^{9,10}

The World Health Organization recommended the integration of the HB vaccine into the national immunization programs in 1992, and global coverage of 3-dose neonatal HBV vaccination reached 79% by 2012.¹⁸

Although the seroconversion rate of hepatitis B vaccine is high, long-term studies have shown that the anti-HBs seropositivity ratio to hepatitis B decreases with age.^{19,20,21} In a 20-year study by Ni et al.,²² the overall seropositivity rate of anti-HBs in 3332 individuals at 20 years of the HBV vaccination was 55.9%.

Kim et al.²³ also reported an overall seropositivity rate of 55.8% in the vaccinated children and young adults (1-27 years). The authors stated that the anti-HBs seropositivity rate reached the highest level (90.0%) at the age of < 12 months. The seropositivity rate was gradually decreased thereafter, reaching the lowest level of 43.5% at the age of 15. It was also speculated that the observed increase in seropositivity rate after age 16 resulted from the anamnestic response to HBV exposure in adulthood.

In our study population of children with cancer, anti-HBs positivity rate was 91% and HBsAg was negative in all patients, with no active HBV infection. This high rate of seroconversion reflects the success of the nationwide vaccination program in implementation since 1998 and the 98% rate of immunization coverage reached by the year 2013.²⁴ Similarly, Igde et al.²⁵ reported an 82.8% anti-HBs seropositivity in 0- to 18-year-old children from the Black Sea region of Turkey. In the era of national vaccination programs, the need for a booster vaccination in a healthy population seronegative for anti-HBs after primary immunization is still a matter of debate. However, booster vaccinations have been recommended for immunocompromised patients, in literature.^{26,27} HBV infections are still endemic in several parts of the world, and considering the frequent transfusions of blood products and significant immunosuppression due to intensive chemotherapies, children with hematologic or oncologic malignancies should be evaluated separately.

The vaccination of special populations, such as patients with primary or acquired immunodeficiencies, children with cancers, recipients of solid organ or hematopoietic stem cell transplantation, and hemodialysis patients, has not been standardized.^{28,29} In a study by Aytac et al.,³⁰ the HBV vaccination of children with juvenile systemic erythematous receiving steroids in a standard schedule (at 0, 1, and 6 months) yielded an 80% seroconversion, and no significant side effects were observed. However, in another study by Yildiz et al.,³¹ lower rate of anti-HBs seroconversion was reported after the vaccination of children with steroid-sensitive nephrotic syndrome.

Vaccination under chemotherapy has been reported to be safe and effective for certain diseases. Vaccines that are based on toxoid, protein subunits, bacterial antigens, or recombinant technology are not contraindicated during chemotherapy. In the case of the HBV vaccination, numerous studies have assessed the efficacy and safety of different booster schedules during cancer therapy, and the level of evidence is now scored as moderately recommended (evidence level B-II).^{13,28}

There is no particular timing and dosing guideline for the vaccination of children with cancer during chemotherapy. The most often used methods for effective vaccination during immunosuppressive therapy are to increase the vaccine dosage and/or the number of doses defined for the immunization of healthy populations. In previous studies, 3 doses

Table 1. Demographic and Clinical Features and Vaccination Responses of Vaccinated Children With Cancer

Patient	Age (years)/Sex	Type of Cancer	Systemic Chemotherapy	Steroid [§]	Lymphocyte/Neutrophil Counts at Vaccination (/mm ³)			Post-vaccination Anti-HBs Titer (IU/L) [¶]
					First dose	Second dose	Third dose	
1	2.3/m	ALL	Prednisolone	Yes	4300/900	600/1000	500/740	>100
2	3.1/f	ALL	Daunorubicin	Yes	800/0	200/300	300/0	77
3	5.7/m	ALL	Vincristine	Yes	800/500	200/1000	440/500	>100
4	6.7/m	ALL	L-asparaginase	Yes	2800/600	300/800	500/300	>100
5	13.6/m	ALL		Yes	8100/2500	1200/2500	600/750	22.9
6	5/f	HL	Adriamycin	No	3200/3500	1800/1300	3400/2700	>100
7	7.5/f	BL	Bleomycin	Yes	7300/1500	100/500	1100/2300	35
8	9.6/m	BL	Vinblastine	Yes	2300/9000	4200/500	2500/3900	>100
9	17.8/m	BL	Dacarbazine Dexamethasone Vincristine Cyclophosphamide Methotrexate Ifosfamide Cytarabine Etoposide	Yes	500/1200	300/1200	100/600	>100
10	7.4/m	RMS	Vincristine Actinomycin-D Cyclophosphamide	No	1000/10 000	2000/300	1800/3500	>100
11	5.6/m	MED	CSRT Vincristine	Yes	4200/5400	3200/3000	1400/1200	>100

[§]Prednisolone with a daily dose of 60 mg/m²/day and dexamethasone 10 mg/kg/day or 0.60 mg/kg/day.

[¶]4-8 weeks after the last dose of vaccination.

m, male; f, female; ALL, acute lymphoblastic leukemia; csrt, cranio-spinal radiotherapy; HL, Hodgkin lymphoma; BL, Burkitt lymphoma; MED, medulloblastoma; RMS, rhabdomyosarcoma.

of booster HBV vaccination were administered with sufficient responses.^{4,14,15,16} We preferred to use a super-accelerated schedule of 4 weeks to reach the protective antibody titers sooner and decrease the risk of treatment incompletion. In our study, all the re-vaccinated patients attained the effective titers after 4–8 weeks of vaccination, and they all remained anti-HBs positive at the end of treatment. Although Köksal et al.¹⁴ and Sodhi et al.¹⁵ reported lower seroconversion rates with this super-accelerated vaccination scheme in comparison to the routine schedule, the previous vaccination status of study populations was not declared in either study. The brisk anamnestic response obtained in our study was probably the result of hepatitis B immunizations in all patients during infancy. Notably, we did not encounter any local and systemic vaccine-related side effect in this very risky patient population.

The reasons for unresponsiveness to HBV vaccination are multifactorial and poorly understood. However, it is speculated that the distribution pattern of peripheral blood lymphocytes in children might be related to a lack of antibody response.^{20,32} In our study, most of the re-vaccinated children had lymphopenia and/or neutropenia during the vaccination period, but they still reached the effective antibody titers. Although it is not possible to state an association due to the small number of patients and the absence of information about the cellular immune status of these patients in infancy, the role of anamnestic response independent of lymphocyte count and the immunologic basis of unresponsiveness to HBV vaccine needs further investigation.

The major limitations of our study are the small number of cases included and the retrospective nature of the study. However, in the presence of an effective national vaccination program and high seroconversion potential of the HBV vaccine, the number is acceptable for a single-center study, and multicenter prospective studies should be designed for better answers.

CONCLUSION

HBV vaccination during intensive chemotherapy is safe and effective in children with cancer. Protective levels of antibody can be obtained in a short period of time, and sustained responses are possible despite related systemic chemotherapy. The super-accelerated schedules we used proved to be effective. However, in future studies, a single-dose booster HBV vaccination might be tested for susceptible children with ongoing cancer treatment, considering the ease of application and compliance.

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