International Journal of Infectious Diseases (2008) **12**, 166—170

http://intl.elsevierhealth.com/journals/ijid

Efficacy of accelerated hepatitis B vaccination program in patients being actively treated for hematologic malignancies

Husnu Pullukcu [a,*], Ekin Ertem [a], Yildiray Karaca [b], Tansu Yamazhan [a], Ruchan Yazan Sertoz [c], İmre Altuglu [c]

[a] *Department of Infectious Diseases and Clinical Microbiology, Ege University Faculty of Medicine, Izmir, Turkey*
[b] *Department of Biochemistry, Aydın Soke Fehime Faik Kocagöz State Hospital, Aydın, Turkey*
[c] *Department of Microbiology and Clinical Microbiology, Ege University Faculty of Medicine, Izmir, Turkey*

Received 7 September 2006; received in revised form 27 April 2007; accepted 18 June 2007
Corresponding Editor: Craig Lee, Ottawa, Canada

KEYWORDS
Accelerated HBV vaccination;
Leukemia;
Lymphoma;
Protection

Summary
Background: The goal of this study was to conduct an accelerated vaccination program and to determine its efficacy in patients susceptible to hepatitis B virus (HBV) receiving chemotherapy because of their hematologic malignancies.
Methods: Over a one-year period, a total of 327 patients who were diagnosed as having a hematologic malignancy were serologically analyzed in terms of HBV infection. Of those found to be susceptible to HBV infection, a total of 42 patients consisting of 16 females and 26 males were enrolled in the accelerated vaccination program. All the patients were administered a 20-μg yeast-derived recombinant hepatitis B vaccine on days 0, 14, and 28. Anti-HBs titers above 10 IU/l at 1 and 3 months after the final dose were accepted as protective.
Results: A total of 146 (44.6%) patients were susceptible to HBV, while 13 (4.0%) were carriers, 28 (8.6%) were vaccinated, and 113 (34.5%) had had a previous HBV infection. A total of 42 patients (16 females and 26 males, mean age 34.5 ± 10.9 years) were enrolled in the vaccination program. Overall, 23.8% (10/42) of the patients in the program had developed anti-HBs at one month after the last vaccination.
Conclusions: Poor results obtained by different vaccination programs suggest the need for alternative strategies to prevent the disease.

Introduction

In patients with a hematologic malignancy, a newly developing infection of hepatitis B virus (HBV) results in the interruption of chemotherapy for a long period, in conjunc-

* Corresponding author. Tel.: +90 232 390 45 10; fax: +90 232 373 45 38.
E-mail address: husnup@yahoo.com (H. Pullukcu).

1201-9712/$32.00
doi:10.1016/j.ijid.2007.06.004

tion with disruption in the management of the primary condition; consequently this results in difficulties in controlling the malignant condition. Patients with a weakened immune system due to chemotherapy develop a more severe clinical picture, which in turn yields to the development of chronic hepatitis B at high rates.[1–5]

HBV reactivation is a described complication in cancer patients who receive cytotoxic chemotherapy, and may result in varying degrees of liver damage.[6] As chemotherapy is used increasingly in cancer patients, HBV reactivation during cytotoxic treatment may become a more common problem. Lok et al. reported that 26% of lymphoma patients had chronic HBV infection and 47% of them developed HBV reactivation during chemotherapy, which resulted in a 5% mortality.[7] In another study, it was stated that while the incidence of chronic HBV was 18% in patients with a hematologic malignancy, the acute exacerbation rate was 37.5% in HBV carriers.[8] Pinto et al. reported acute exacerbation in five patients with hematologic malignancy and HBV infection, and four of them died.[9] Studies conducted on adult patients with hematologic malignancies show that HBV carrier status reaches rates of over 20% in our country.[10,11] HBV carriers have the risk of fatal HBV exacerbation during chemotherapy/radiotherapy.[10–14]

In HBV reactivation, two possible mechanisms may be involved. While immunosuppression during chemotherapy may allow enhanced HBV replication and thereby lead to direct hepatic toxicity, the overt exacerbation of hepatitis is more likely to be a result of a rebound immune response. The latter is explained by the fact that the administration of immunosuppressive agents results in T lymphocyte depletion, and this suppresses the normal immunological response to viral antigens and allows widespread infection of hepatocytes.[8,14,15]

In patients with a diagnosis of hematologic malignancy, chemotherapy is introduced at the earliest period in order to achieve an early remission. This is the period in which the patients are most susceptible to HBV infection. Hence, the determination of HBV status at the time of diagnosis of the malignancy and the immunization of susceptible subjects with an active vaccination schedule is of crucial importance.[1]

The goal of this study was to search for the indicators of HBV infection, to conduct an accelerated vaccination program on the susceptible patients, and to determine the efficacy of vaccination in patients receiving chemotherapy because of their hematologic malignancies.

Materials and methods

The study group

Three hundred and twenty-seven patients who had been followed up for various hematologic malignancies between April 2003 and April 2004 were prospectively included in the study. The study was started with the approval of the local ethics committee. Informed written consent was obtained from each patient. Patients were grouped according to the results of HBV serologic marker testing. HBV carriers, patients who had previously had the infection, those who had previously been vaccinated, and patients with an isolated anti-HBc positivity were excluded. The clinical condition of each patient was evaluated by the Eastern Cooperative Oncology Group (ECOG) performance status scoring system, and those with an ECOG score over three were excluded from the study.[16] There was no plan for an autologous/allogeneic bone marrow transplantation for any of them within the next month.

Serologic examinations

A blood specimen of 10 ml was taken from each patient in order to perform the serologic tests for HBV (HBsAg, anti-HBc total, and anti-HBs). All of the HBV markers were studied using enzyme immune assays (HBsAg IEMA WELL, anti-HBs IEMA WELL, anti-HBc EIA WELL; Radim, Rome, Italy). A 20-μg recombinant hepatitis B vaccine derived from yeast cells was administered to each patient on days 0, 14, and 28 (a total of three doses) by intramuscular route into the deltoid muscle. One and three months after the last dose of vaccine, HBV markers were re-examined to search for the emergence of anti-HBs, and also to detect the development of a possible acute HBV infection. Anti-HBs levels were assayed through titrimetric analyses, and titers >10 IU/l were accepted as protective. Throughout the study period, all patients had normal liver function test values.

Statistical analysis

Data obtained were recorded and evaluated in SPSS 11.0 package program. Fisher's exact and Chi-square tests were used for statistical comparisons.

Results

The primary diagnoses and HBV status characteristics of the 327 patients (182 male and 145 female, mean age 48.4 ± 17.4 years) are shown in Tables 1 and 2.

Forty-two of the 146 HBV sensitive patients accepted enrollment in the vaccination program (16 female and 26 male, mean age 34.5 ± 10.9 years; Table 3). All of the patients were receiving chemotherapy. The patients' average ECOG score was 1.5 ± 0.7 (one patient got 0 points, 22 patients got 1 point, 15 patients got 2 points, and four

Table 1 Distribution of patients according to diagnosis and gender

Diagnosis	Male	Female	Total
Non-Hodgkin lymphoma	53	34	87
Acute myelocytic leukemia	38	39	77
Multiple myeloma	33	32	65
Hodgkin lymphoma	15	12	27
Acute lymphocytic leukemia	15	10	25
Mycosis fungoides	8	7	15
Myelodysplastic syndromes	6	4	10
Hairy cell leukemia	6	1	7
Chronic lymphocytic leukemia	2	5	7
Chronic myelocytic leukemia	5	1	6
Acute leukosis	1	-	1
Total	182	145	327

Table 2 HBV status by patient age and gender

Age groups	Female							Male							Total
	15–20	21–30	31–40	41–50	51–60	>60	Female total	15–20	21–30	31–40	41–50	51–60	>60	Male total	
Sensitive	4	6	12	11	12	13	58	8	16	12	16	18	18	88	146 (44.6%)
Carrier	1		2	2	1	1	7		1	2		2	1	6	13 (4.0%)
Vaccinated	3		2	2	3	4	14	3	2	1	4	2	2	14	28 (8.6%)
Past infection	3	3	8	13	11	14	52	4	5	7	16	11	18	61	113 (34.5%)
IaHBc positivity[a]		2		3	3	6	14		1	1	1	5	5	13	27 (8.3%)
Total	11	11	24	31	30	38	145	15	25	23	37	38	44	182	327

[a] IaHBc: isolated anti-HBc positivity.

Table 3 Distribution of age, gender, and clinical diagnosis for the patients enrolled in the vaccination program

Clinical diagnosis	Female						Male						Total
	Age					Female total	Age					Male total	
	15–20	21–30	31–40	41–50	51–60		15–20	21–30	31–40	41–50	51–60		
Non-Hodgkin lymphoma			4	1	1	6	2	3	2	1		8	14
Acute myelocytic leukemia	1	1		1		3		2	1	1		4	7
Hodgkin lymphoma		1	1			2		2		2		4	6
Multiple myeloma				1		1			1	2	1	4	5
Acute lymphocytic leukemia	1	1	1			3			1			1	4
Chronic myelocytic leukemia								1	2			3	3
Chronic lymphocytic leukemia										1		1	1
Hairy cell leukemia									1			1	1
Myelodysplastic syndromes					1	1							1
Total	2	3	6	3	2	16	2	8	8	7	1	26	42

patients got 3 points). All the patients completed the vaccination program.

Overall, 23.8% (10/42) of the patients in the program had developed >10 IU/l anti-HBs at one month after the last vaccination (two with non-Hodgkin lymphoma, two with acute myelocytic leukemia, one with multiple myeloma, one with Hodgkin lymphoma, two with acute lymphocytic leukemia, one with a myelodysplastic syndrome, and one with chronic lymphocytic leukemia). Antibody production was detected in 43.7% (7/16) of the female patients and in 11.5% (3/26) of the males ($p = 0.035$). Titrimetric anti-HBs values ranged between 10 and 100 IU/l.

Due to a decrease in antibody titers (to <10 IU/l), 19.0% of the patients were anti-HBs positive at the third month following the last vaccination.

When questioned about any adverse effects of the vaccine, no serious side effect was notified except for local pain in the arm where the vaccine was applied. None of the patients developed an acute HBV infection throughout the vaccination and follow-up period.

Discussion

Patients with hematologic malignancies are at risk for HBV infection not only due to the immunodeficiency arising as a result of the primary disease and bone marrow suppression secondary to chemotherapy and radiotherapy, but also due to the frequent blood transfusions and interventional procedures employed. Since our country is an intermediate endemic region for HBV infection and high rates of horizontal transmission are being observed, it has become necessary to study this particular patient group.[1,17]

A wide range of studies conducted in our country on healthy adults and children have shown the rates of HBV carrier status ranging between 3.9% and 12.5%.[18] In studies designed to detect the HBV seroprevalence among patients with hematologic malignancies, rates of carrier status among children have been found to range between 6% and 57.2%, whereas rates among adults have been found to range between 6% and 40.6%.[1,2,18,19] Anti-HBs positivity rates in the same adults have been detected between 31.4% and 33.3%.[1,2,18,19] The rates reported in these studies are similar to those reported for healthy individuals. However it is also known that there is not much difference in HBV infection rates between the risk groups such as, healthcare workers, dialysis patients, etc., and the normal population in moderately or highly endemic areas.[20] In our study, the carrier status rate in 327 patients with a hematologic malignancy was detected as 4%. When HBsAg, anti-HBc, and anti-HBs markers were also considered, the exposure rate to HBV reached 46.5%.

The overall anti-HBs positivity rate was 23.8% at the end of our accelerated vaccination program. Antibody production was detected in 43.7% of the female patients and in 11.5% of the male patients. In vaccination studies conducted in healthy adults, it has been recognized that women develop antibody responses in higher titrations than men.[21–23] Three months after the vaccination program, anti-HBs titers in one male and one female patient decreased below detection limits. Pressure on immunity in these patients can cause the antibody titers determined at the beginning to fall under the levels to be determined later on.

To our knowledge, no accelerated hepatitis B vaccination study conducted on adult patients with hematologic malignancies exists. This has brought difficulties in the interpretation of our results. There are various publications analyzing the efficacy of different vaccination programs on pediatric patients receiving chemotherapy due to their hematologic malignancies. It has been reported in India that in children and young adults, anti-HBs seroconversion rates are between 19% and 36%.[24,25] In our country, Yetgin et al. achieved an anti-HBs positivity rate of 35% in children with hematologic malignancies, following a vaccination program in which increased numbers of doses (each being 20 μg) were administered.[26] In a study from our region including 36 pediatric cases with different malignancies, an anti-HBs seroconversion rate of 61% was obtained after the application of seven double-dose vaccines. In this study, it was reported that the antibody response was obtained in all of the patients who had received maintenance chemotherapy.[27] Our vaccination program appears to be more advantageous owing to the ability to attain a quick antibody response.

During the study period, liver function tests were carried out twice weekly on a regular basis. No clinical and serologic acute HBV infection was detected in the patients. In an earlier study, despite active immunization, acute hepatitis B infection was reported to develop in 5.6% of patients who had failed to show anti-HBs seroconversion.[27] The low seroprevalence of hepatitis B in our region may have played a partial role in this phenomenon.[18] Regarding the presence of HBV carrier status in up to 20% in the eastern regions of our country, we consider that if similar studies were conducted in these regions on patients with hematologic malignancies, even higher rates of HBV exposure would have been detected. Likewise, in India, Goyal et al.[24] reported that HBV developed in 48% of patients who had been taken into a vaccination program during remission induction therapy, and Somjee et al.[25] reported a 43% HBV occurrence rate in their patients.

Each day, new chemotherapy regimens are introduced for the management of patients with hematologic malignancies and for patients with other solid tumors. With these new therapies we can predict that the survival rates of these patients will even increase in the near future. Moreover, in recent years, a rapid increase has been observed in the number of immunocompromised patients due to conditions such as transplantation and HIV positivity. This results in the formation of a high-risk group for HBV infection. In the light of this fact, it has been understood that vaccination studies against HBV infection in immunocompromised patients will become even more important in the forthcoming years.

In conclusion, the high prevalence of HBV infection in patients with hematologic malignancies and the poor results obtained from different vaccination programs suggest the need for alternative strategies to prevent the disease. We believe that active immunization combined with hepatitis B immunoglobulin given simultaneously may yield better response rates and reduce the endemicity of HBV infection in this particular group of patients. Therefore, further studies aimed at investigating the role and effectiveness of combined immunoprophylaxis regimens on wider groups with longer follow-up periods are needed.

Conflict of interest: No conflict of interest to declare.

References

1. Besisik F, Besisik FS. [The problem of chronic viral hepatitis in the immune compromised] (in Turkish). In: Tabak F, Balık İdt, Tekeli E, editors. *Viral hepatit 2005*. İstanbul: Viral Hepatitle Savaşım Derneği; 2005. p. 90—102.
2. Trotter JF. Rapidly progressive hepatitis C mimicking extrahepatic biliary obstruction in non-hepatic solid organ transplant recipients. *Hepatology* 1997;**24**(Suppl):145A.
3. Delladetsima JK, Boletis JN, Makris F, Psichogiou M, Kostakis A, Hatzakis A. Fibrosing cholestatic hepatitis in renal transplant recipients with hepatitis C virus infection. *Liver Transpl Surg* 1999;**5**:294—300.
4. Flowers MA, Heathcote J, Wanless IR, Sherman M, Reynolds WJ, Cameron RG, et al. Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. *Ann Intern Med* 1990;**112**: 381—2.
5. Yeo W, Zee B, Zhong S, Chan PK, Wong WL, Ho WM, et al. Comprehensive analysis of risk factors associating with hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Cancer* 2004;**90**:1306—11.
6. Lau JY, Bird GL, Gimson AE, Alexander GJ, Williams R. Treatment of HBV reactivation after withdrawal of immunosuppression. *Lancet* 1991;**337**:802.
7. Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. *Gastroenterology* 1991;**100**:182—8.
8. Yeo W, Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 2000;**62**:299—307.
9. Pinto PC, Hu E, Bernstein SM, Pinter BL, Govindarajan S. Acute hepatic injury after the withdrawal of immunosuppressive chemotherapy in patients with hepatitis B. *Cancer* 1990;**65**:878—84.
10. Sari R, Ozkan HI, Sevinc A, Aydogdu I. [Seropositivity of hepatitis B and hepatitis C viruses in blood and blood products in transfused and non-transfused patients with hematological malignancies] (in Turkish). *Turgut Ozal Tip Merkezi Dergisi* 2000;**7**: 109—12.
11. Cengiz AT, Kiyan M, Uysal VA, Ugurel MS. [Investigation of HBsAg in the sera of patients with Hodgkin's disease, non-Hodgkin lymphoma and leukemia] (in Turkish). *Turk J Infect* 1992;**6**: 257—60.
12. Haydon GH, Mutimer DJ. Hepatitis B and C virus infections in the immune compromised. *Curr Opin Infect Dis* 2003;**16**:473—9.
13. Xunrong L, Yan AW, Liang R, Lau GK. Hepatitis B virus (HBV) reactivation after cytotoxic or immunosuppressive therapy—pathogenesis and management. *Rev Med Virol* 2001;**11**:287—99.
14. Liaw YF. Hepatitis viruses under immunosuppressive agents. *J Gastroenterol Hepatol* 1998;**13**:14—20.
15. Steinberg JL, Yeo W, Zhong S, Chan JY, Tam JS, Chan PK, et al. Hepatitis B virus reactivation in patients undergoing cytotoxic chemotherapy for solid tumours: precore/core mutations may play an important role. *J Med Virol* 2000;**60**:249—55.
16. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Gr*oup. *Am J Clin Oncol* 1982;**5**:649—55.
17. François G, Hallauer J, Van Damme P. Hepatitis B vaccination: how to reach risk groups. *Vaccine* 2002;**21**:1—4.
18. Mistik R, Balik İ. [The analysis of viral hepatitis in Turkey.] Viral hepatit is] 2003 Tekeli E, Balık İ (Eds), Viral Hepatitle Savaşım Derneği 2003, sayfa:10—55.
19. Akyol H, Sarialioglu F, Buyukpamukcu M, Karadeniz C, Akyuz C, Kutluk T. Hepatitis-B Virus infections in pediatric patients receiving anti-cancer chemotherapy. *Turk J Cancer* 1990;**3**:104—8.
20. Tasyaran MA. [Epidemiology of HBV infections] (in Turkish). In: Tekeli E, Balik I, editors. *Viral hepatit 2005*. Istanbul: Viral Hepatitle Savasim Dernegi; 2003. p. 121—9.
21. Heron LG, Chant KG, Jalaludin BB. A novel hepatitis B vaccination regimen for adolescents: two doses 12 months apart. *Vaccine* 2002;**20**:3472—6.
22. Hosoglu S, Ayaz C, Ozen A, Kokoglu OF, Geyik MF. [Influence of factors on antibody response to hepatitis B vaccination] (in Turkish). *Viral Hepatit Dergisi* 1997;**1**:38—41.
23. ul-Haq N, Hasnain SS, Umar M, Abbas Z, Valenzuela-Silva C, Lopez-Saura P. Immunogenicity of 10 and 20 microgram hepatitis B vaccine in a two-dose schedule. *Vaccine* 2003;**21**:3179—85.
24. Goyal S, Pai SK, Kelkar R, Advani SH. Hepatitis B vaccination in acute lymphoblastic leukemia. *Leuk Res* 1998;**22**:193—5.
25. Somjee S, Pai S, Kelkar R, Advani S. Hepatitis B vaccination in children with acute lymphoblastic leukemia: result of an intensified immunization schedule. *Leuk Res* 1999;**23**:365.
26. Yetgin S, Tunc B, Koc A, Toksoy HB, Ceyhan M, Kanra G. Two booster dose hepatitis B virus vaccination in patients with leukemia. *Leuk Res* 2001;**25**:647—9.
27. Ucar C, Oren H, Uysal K, Gulen H, Duman M, Irken G. [The resultsof hepatitis B vaccination in the patients with hematologic malignancies followed in Dokuz Eylul University Faculty of Medicine hematology unit] (in Turkish). *Dokuz Eylul Universitesi Tip Fakultesi Dergisi* 2001;**15**:11—5.