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Prevention of Hepatitis B Reactivation With Lamivudine in Hepatitis B Virus Carriers With Hematologic Malignancies Treated With Chemotherapy—A Prospective Case Series

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Administration of immunosuppressive treatment in hepatitis B virus carriers with malignancies is associated with the risk of hepatitis B reactivation. This complication is more frequent in patients with hematologic malignancies because administration of corticosteroids, the mainstay of treatment of these patients, is an independent risk factor for hepatitis B reactivation. When lamivudine is given prior to chemotherapy, it prevents the viral replication during the immunosuppression period; therefore, it might reduce the risk of hepatitis B exacerbation. We performed a prospective study to assess the efficacy of prophylactic administration of lamivudine in this setting. Ten hepatitis B virus carriers with hematologic malignancies were included in this study; seven were HBsAg positive, and three had isolated antiHBc and detectable HBV-DNA levels. Nine patients were given corticosteroids after the administration of lamivudine. Lamivudine was given per os at a dose of 100 mg once daily. In four patients that had not been previously treated with chemotherapy, lamivudine was started 19 days (median) (range, 0–35 days) prior to the onset of chemotherapy. The administration of lamivudine has not stopped since in any of our patients. After a median follow-up of 15 months (range 6–38 months), no hepatitis B reactivation was observed. HBV-DNA levels were decreased in all 6 patients who had detectable HBV-DNA at baseline. Lamivudine was well tolerated. Chemotherapy regimens were administered as planned, and their effectiveness was not compromised by lamivudine. In conclusion, prophylactic administration of lamivudine should be considered as a means of reducing the frequency of hepatitis B reactivation in hepatitis B virus carriers with hematologic malignancies who are being treated with chemotherapy. Am. J. Hematol. 80:197–203, 2005. © 2005 Wiley-Liss, Inc.

Key words: chemotherapy; hematologic malignancies; hepatitis B reactivation; lamivudine

INTRODUCTION

Immunosuppressive treatment in hepatitis B virus (HBV) carriers with malignancies is associated with the risk of reactivation of hepatitis B in 38–78% of them [1–5]. The liver damage that is caused is characterized by varying degrees of severity, including jaundice and fatal hepatic failure in 10–63% and 4–71% of the cases, respectively [1,4–7]. It may also cause delays or modifications of therapy or even its cessation [4,8].

This complication is more frequent in patients with hematologic malignancies because administration of corticosteroids, the mainstay of treatment of these patients, is an independent risk factor for HBV reactivation [2,4,9,10]. The administration of more intensive chemotherapy in order to treat the non-responders also increases the frequency of hepatitis B flare-up [1,11].

Hepatitis B is a major health problem with 350 million people infected worldwide, while in endemic areas the carrier rate of the population is as high as

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15–20% [7,9]. Therefore, patients with hematologic malignancies might also be HBV carriers with a frequency as high as 26% [3]. Hepatitis B is endemic in Greece; 5.4% of Greek patients with solid tumors are HBsAg carriers [12].

Lamivudine (the negative enantiomer of 3′-thiacytidine, 3-TC), a reverse transcriptase inhibitor initially approved for antiviral therapy in HIV infection, effectively inhibits HBV replication in chronic hepatitis B [13–15]. It is well tolerated and has little if any hematologic toxicity [13,15–17]. It has been shown to be effective in the management of chemotherapy-induced HBV reactivation in patients with hematologic malignancies; nevertheless, mortality rates might still be high if treatment is delayed or if there is already a high viral load in the liver [7,11,13,18–20]. When lamivudine is given prior to chemotherapy, it prevents the HBV replication during the immunosuppression period, and thus might reduce the risk of hepatitis B exacerbation. However, there are only a few reports about the prophylactic administration of lamivudine in this setting [7,8,20–24].

We report our experience on the effectiveness of the prophylactic administration of lamivudine in ten HBV carriers with hematologic malignancies.

MATERIALS AND METHODS

All patients diagnosed with hematologic malignancies in our Department who were also either hepatitis B virus surface antigen (HBsAg) positive or had isolated antibody against hepatitis B core antigen (antiHBc) along with detectable HBV-DNA were systemically identified and included in the study. We initiated this prospective study on November 2000 at Hippokration General Hospital of Thessaloniki, a tertiary teaching hospital. The study was approved by the ethics committee of our institution, and all patients provided written informed consent. The study was performed in accordance with the principles of the Declaration of Helsinki.

Before the administration of lamivudine, the following examinations were performed: (a) evaluation of liver function by testing alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (γGT), alkaline phosphatase (ALP), bilirubin (total, direct, indirect), prothrombin time, total protein, albumin, and globulins. These tests were performed before every chemotherapy cycle, every month after the last cycle, and when there were indications of acute hepatitis; (b) test for the presence of HBsAg, antibody against HBV surface antigen (antiHBs), antiHBcIgG, antiHBcIgM, HBV antigen e (HBeAg), antibody against HBeAg (antiHBe), and HBV-DNA [this was measured using polymerase chain reaction (PCR) (Amplicor HBV-DNA Monitor Test; Roche Diagnostics, Branchburg, NJ) with sensitivity of 400 copies/mL]; these tests were performed at baseline, every 3 months, and when there were clinical or laboratory indications of acute hepatitis B; and (c) tests for the presence of IgG and IgM antibodies against the following viruses: hepatitis A (HAV), Ebstein-Barr (EBV), cytomegalovirus (CMV), and herpes simplex virus (HSV) I and II, and also for hepatitis C (HCV), delta (HDV), and human immunodeficiency virus (HIV). These tests were performed at baseline and when there were clinical or biochemical indications of acute hepatitis.

Patients with acute hepatitis, pancreatitis, or chronic liver failure at the initiation of treatment or with any condition contraindicating the use of chemotherapy were excluded from the study.

Reactivation of hepatitis was defined clinically, biochemically, and virologically. Clinical and biochemical definition of reactivation included the appearance of jaundice and a more than 10-fold elevation of AST and ALT activity compared to baseline levels. Fulminant hepatitis was defined as the appearance of acute liver disease with jaundice and hepatic encephalopathy. Asymptomatic reactivation was defined as the virologic reactivation with less than a 10-fold increase of aminotransferase activity compared to baseline levels without any clinical signs of liver disease. Virologically, reactivation was defined as an increase in HBV-DNA levels more than 400 copies/mL for patients with undetectable viral load prior to the exacerbation or as a more than 10 times increase compared to pre-exacerbation levels [25].

Other possible causes of acute liver disease were excluded in each case of reactivation with serological testing for HAV, HCV, HDV, EBV, CMV, and HSV I and II. We had to rely on serological criteria to diagnose viral reactivation because more sensitive tests (such as quantitative PCR, CMV early antigen detection, and CMV antigenemia assays) were not routinely performed at our Institution during the initiation of our study. The presence of infection, drug toxicity, and liver involvement by the hematologic malignancy were also excluded. Reactivation was considered to be caused by immunosuppressive treatment if it occurred up to 4 months after its withdrawal and spontaneous if it occurred later.

Lamivudine was given per os at a dose of 100 mg, once daily, if creatinine clearance was above 50 mL/min. Breakthrough infection with lamivudine-resistant mutants was defined as reappearance of serum HBV-DNA after its initial disappearance.

TABLE I. Characteristics of Patients at Baseline*

Patient no.	Age (years)	ALT (U/L)	HBV DNA (copies/mL)	HBsAg	antiHBc	HBeAg	antiHBe	Hematologic malignancy
1	77	71	NP	Positive	Positive	Negative	Positive	NHL
2	73	NV	1×10^7	Positive	Positive	Positive	Negative	CLL
3	25	168	<400	Positive	Positive	Negative	Positive	ALL
4	65	65	2.8×10^3	Negative	Positive	Negative	Negative	CLL
5	56	NV	<400	Positive	Positive	Negative	Positive	AA
6	52	NV	1.6×10^3	Positive	Positive	Negative	Positive	NHL
7	47	NV	<400	Positive	Positive	Negative	Positive	WM
8	64	NV	1.1×10^3	Negative	Positive	Negative	Negative	AML
9	62	NV	6.4×10^2	Negative	Positive	Negative	Negative	CLL
10	71	NV	1.6×10^3	Positive	Positive	Negative	Positive	NHL

*Abbreviations: NHL, non-Hodgkin lymphoma (high grade); CLI, chronic lymphocytic leukemia; ALL, acute lymphoblastic leukemia; AA, aplastic anaemia; WM, Waldenström macroglobulinemia; AML, acute myeloid leukemia; NV, normal values; NP, test not performed.

RESULTS

Ten patients were included in the study, and their characteristics are shown in Table I. These 10 patients were inclusive of all at-risk patients during the study period. All except for one were male, with a median age of 63 years (range 25–77 years). Three patients had elevated ALT levels at baseline (median level 71 U/L, range 65–168 U/L), due to prior administration of chemotherapy. Three patients were only antiHBc positive. One patient was HBeAg positive. This patient, as well as two out of six HBeAg negative patients, had detectable HBV-DNA. There were no data on the HBV-DNA levels for one patient while the three patients with isolated antiHBc positive had by definition detectable HBV-DNA. Median HBV-DNA levels were 1100 copies/mL (range 640–10^7 copies/mL). None of the patients was HIV or HCV positive. The most frequent malignancies were chronic lymphocytic leukemia and non-Hodgkin lymphoma (3 cases each). Six patients had been treated with chemotherapy prior to the initiation of lamivudine, which included corticosteroids in 4 of them; none of the patients had shown an increase in ALT levels prior to the initiation of this study. Nine patients were given corticosteroids after the administration of lamivudine. Four patients were treated with rituximab (patients 1, 2, 6, and 7 in Tables I and II); patient 6 received combination treatment with rituximab and conventional chemotherapy, whereas patients 1, 2, and 7 received rituximab monotherapy as second-line treatment.

Lamivudine was given per os at a dose of 100 mg, once daily, as creatinine clearance was above 50 mL/min in all patients. In four patients that had not been previously treated with chemotherapy, lamivudine was started 19 days (median) (range 0–35 days) prior to the onset of chemotherapy. Administration of lamivudine has not stopped since in any of our patients.

TABLE II. Results of Treatment at the End of Follow-up*

Patient no.	ALT (U/L)	HBVDNA (copies/mL)	Response to chemotherapy †	Follow-up (months)
1	NV	5.4×10^2	CR→RE→death	16
2	NV	1.3×10^5	PR	38+
3	81	<400	CR	30+
4	NV	<400	PR	29+
5	NV	<400	Death	12
6	NV	<400	CR	17+
7	NV	<400	PR	14+
8	NV	<400	PR→RE→death	9
9	NV	<400	PR→RE→death	12
10	NV	<400	PR	6+

*Abbreviations: NV, normal values; CR, complete response; RE, relapse; PR, partial response.

Results are shown in Table II. Lamivudine was not stopped in any of the patients, and it was well tolerated. Chemotherapy regimens were administered as planned. Two patients exhibited complete response, four exhibited partial response, one relapsed and died after an initial complete response, two relapsed and died after an initial partial response, and one did not respond to chemotherapy and died. None of the patients exhibited HBV reactivation during the study period.

At their last examinations, nine patients had normal aminotransferase levels while HBV-DNA levels were decreased in all patients who had detectable HBV-DNA at baseline. Except for patient 2, HBV-DNA became undetectable by PCR 3 months after the initiation of lamivudine administration. Hepatitis B serology remained unchanged in all patients during the entire study period; all seven HbsAg-positive patients at baseline continued to remain positive during the study period.

After a median follow-up of 15 months (range 6–38 months), four patients demonstrated a transient slight increase of aminotransferase levels during the treatment

that was attributed to chemotherapy toxicity; reactivation of HBV infection and all other possible causes of acute liver disease were excluded thoroughly in all these patients.

Patient 2, despite treatment with lamivudine for 25 months, had persistently high HBV-DNA levels and did not show seroconversion (he remained HBeAg positive and antiHBe negative). He was placed on interferon A/2α 3×10^6 IU three times per week along with lamivudine. He received combined treatment for 14 months, but HBV-DNA levels exhibited only transient decreases. Therefore, interferon was discontinued, and he was recently placed on adefovir dipivoxil along with lamivudine. It should be noted that, despite the administration of multiple chemotherapy regimens and the lack of control of viral replication in this patient with the antiviral agents mentioned above, aminotransferase levels exhibited only slight (less than 2 times the upper normal limits) and transient increases throughout a follow-up time of more than 3 years.

Patients were treated with lamivudine for the entire follow-up time (median 15 months, range 6–38 months) and are still receiving lamivudine; during this time, no case of breakthrough infection was observed. Except for patient 2, none of the remaining patients received any anti-HBV agents during the study period.

DISCUSSION

Reactivation of hepatitis B in patients with chronic HBV infection is part of the natural history of the infection and can occur spontaneously, without any apparent cause, with an estimated annual incidence of 7.3% [26,27]. Administration of chemotherapy to patients with malignancies who are also carriers of HBV, by means of the subsequent immunosuppression, promotes viral replication and infection of a substantial number of hepatocytes. After the withdrawal of chemotherapy, partial recovery of cytotoxic T-cell-mediated immune response causes rapid destruction of the infected hepatocytes [20]. This complication has been well known for over 25 years and poses a major risk for these patients, with varying morbidity and mortality rates [1,2,17,28–32]. The severity of the subsequent liver damage cannot be predicted and may range from slight elevation of aminotransferases to fatal fulminant hepatitis [13,20,33].

Until recently, treatment of hepatitis B flare-up had included supportive care only, while plasma exchange, corticosteroids, and interferon had exhibited limited efficacy [11]. Recently, lamivudine has been successfully used in this setting, but experience is limited [11,13,18,19]. Some suggest that prompt diagnosis of hepatitis B exacerbation and early commencement of lamivudine therapy will decrease morbidity and mortality. In one study, however, despite the administration of lamivudine within 2 days after the diagnosis of hepatitis B flare-up, 67% of the patients who developed reactivation died [7]. One possible explanation is that, although lamivudine suppresses HBV replication, the presence of a high viral load in the liver before its administration inevitably leads to massive liver necrosis.

To date, available strategies for the prevention of HBV reactivation were scarce and lacked effectiveness and documentation. It has been proposed that these patients be treated with reduced-intensity chemotherapy, but the risk of flare-up still exists and the likelihood of remission is obviously diminished [13]. Some suggest the administration of steroid-free chemotherapy, but these regimens are considered suboptimal and hepatitis exacerbation can develop even in these patients [20,23,35]. Interferon has been used in a few cases, but is often prematurely withdrawn because of its hematologic toxicity. More importantly, it appears to lack efficacy in the prevention of HBV reactivation, especially in immunosuppressed patients [8,13,20,23,34–38]. One of our patients, due to a lack to response to lamivudine, was given interferon, but he did not respond. There is only one report on the prophylactic administration of famciclovir in eight patients who received allogeneic bone marrow transplantation; one of these patients experienced hepatitis flare-up in spite of famciclovir administration [39].

Prophylactic administration of lamivudine has been implemented in only 14 patients who had non-Hodgkin lymphoma and chronic hepatitis B and who were treated with autologous bone marrow transplantation or conventional cytotoxic agents. Lamivudine was started during chemotherapy and for 4–18 months after its completion and prevented hepatitis B flare-up without affecting peripheral blood stem cells harvesting without causing modifications in the chemotherapy regimens or affecting their effectiveness or hematological recovery after their completion [13,18,20–23]. In a single study, lamivudine was given before the onset of chemotherapy and for 1 month after its withdrawal in 20 patients with lymphoid malignancies, and it showed similar results without any adverse effects [8]. There are also three studies in which lamivudine was given to 39 patients with various malignancies, prior to the commencement of chemotherapy, and was continued for 6–12 months after its completion; no hepatitis B flare-ups occurred [7,24,40]. In a recent report, lamivudine showed similar results when administered to 10 children with hematologic malignancies who had suffered in the

past immunosuppressive-induced hepatitis B virus reactivation [41].

Our study confirms the effectiveness of prophylactic administration of lamivudine in preventing hepatitis exacerbation in patients with chronic hepatitis B who are being treated with chemotherapy for hematologic malignancies. Viral replication was suppressed by lamivudine and this resulted in a reduction or normalization of aminotransferase and HBV-DNA levels.

Nine out of 10 patients in our study received corticosteroids as a part of the chemotherapy regimen, and none experienced HBV reactivation. Corticosteroids are the most significant predisposing factor to HBV reactivation, because they promote viral replication both directly and indirectly by causing immunosuppression [4]. In a comparative trial, flare-ups occurred in 47.4% compared 8.3% in HBV carriers with non-Hodgkin lymphoma treated with corticosteroids-containing and corticosteroids-free chemotherapy, respectively [9].

Male sex is also an independent risk factor for HBV reactivation [3,5], but, even though all our patients except for one were male, flare-ups did not occur. The majority of our patients was treated with second- or third-line chemotherapy regimens, due to lack of response to the first-line ones; nevertheless, the intensification of cytostatic treatment, a known risk factor for HBV reactivation [1–11], did not lead to flare-ups, further supporting the efficacy of lamivudine in this setting. Finally, 4 patients were treated with rituximab, the administration of which has been recently associated with the occurrence of fulminant hepatitis caused by HBV reactivation [42]. We are among the first to report the prevention of hepatitis B flare-up with lamivudine in patients treated with rituximab.

Most cases of HBV reactivation occur after the first two or three chemotherapy cycles [7,18]. Lamivudine can suppress viral replication as early as 1 week after its commencement. Therefore, it can be started close to chemotherapy thus avoiding delays in the beginning of treatment [7]. Our study confirms this hypothesis.

Since hepatitis flare-ups might occur as late as 90–105 days after withdrawal of chemotherapy [4,7], lamivudine should be given for a longer period of time and maybe indefinitely. Nevertheless, long-term administration of lamivudine is associated with rise of resistant HBV mutants in 40% of the patients after 1 year and even more frequently in more prolonged treatment [15,34]. This is caused by mutations in the YMMD (tyrosine, methionine, aspartate, aspartate) motif of the active site of the virus DNA polymerase [43]. The clinical significance of this phenomenon, in view of the fact that these strains are less replication-competent in vitro than wild-type HBV, remains to be elucidated [34]. None of our patients showed evidence of a breakthrough infection despite the protracted administration of lamivudine.

Patients with negative serologic markers of hepatitis B but with detectable HBV-DNA and also patients with immunity against HBV due to past exposure (antiHBs positive and antiHBc positive) are also at risk of developing hepatitis B flare-up once they are treated with chemotherapy. Therefore, they should be monitored closely or even given lamivudine [4,13,44–46]. This is the first report on the pre-emptive administration of lamivudine in HBsAg-negative and antiHBc- and HBV DNA-positive patients with hematologic malignancies.

Lamivudine might cause transient asymptomatic elevations of amylase, lipase, and creatine phosphokinase levels in some patients; this side effect lacks clinical significance. Generally, incidence of its adverse events was similar to that of placebo in most trials [34]. In our patient cohort, no adverse effects associated with the administration of lamivudine were observed.

Our study has a few limitations. First, a truly pre-emptive approach was not implemented in all our patients; this happened because prophylactic administration of lamivudine in these patients is a rather novel modality and therefore some of our patients with chronic HBV infection were already being treated with chemotherapy. Secondly, we chose to determine HBV-DNA levels every 3 months and not more frequently. This was done because this would significantly increase cost without altering our treatment strategy. Furthermore, viral kinetics in these patients is largely unknown and the optimal interval of HBV-DNA determination has not been clarified. It is therefore possible that some HBV reactivations could have been missed. Nevertheless, the latter were obviously asymptomatic and possibly insignificant.

In conclusion, all patients with hematologic malignancies should be tested for serologic markers of hepatitis B. Those who are HBsAg carriers, or antiHBc positive with detectable HBV-DNA, should be given lamivudine prior to chemotherapy and at least for 6 months after its withdrawal. The optimal duration of treatment and the role of new nucleoside analogues such as adefovir dipivoxil in patients that develop resistant HBV mutants remain to be evaluated in prospective large-scale studies.

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