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Original article

Prevention of hepatitis B reactivation with lamivudine in hepatitis B virus carriers with hematologic malignancies treated with chemotherapy

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SUMMARY

Background: 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. Aim: To assess the efficacy of prophylactic administration of lamivudine in this setting. Methodology: Ten hepatitis B virus carriers with hematologic malignancies were included in the 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 who 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 been stopped since in any of our patients. Results: 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 six 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. Conclusion: Prophylactic administration of lamivudine is a safe and effective method to reduce the frequency of hepatitis B reactivation in hepatitis B virus carriers with hematologic malignancies, who are being treated with chemotherapy.

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

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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 cases.[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 necessitate 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 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 on 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 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 included in the study. We initiated this study on November 2000 at Hippokration General Hospital of Thessaloniki, a tertiary teaching hospital. Informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Helsinki Declaration.

Prior to 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, 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) with sensitivity of 400 copies/ml]. These tests were performed on baseline, every three 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 on baseline and when there were clinical or biochemical indications of acute hepatitis.

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

Reactivation of hepatitis was defined clinically, biochemically and serologically. 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 serological reactivation with less than a 10-fold increase of aminotransferase activity compared to baseline levels without any clinical signs of liver disease. Serologically, 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-fered increase compared to pre-exacerbation levels.

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. 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 when it occurred up to 4 months after its withdrawal and spontaneous if it occurred later than 12 months after its withdrawal.

Ten patients were included in the study and their characteristics are shown in Tables 1 and 2. All except 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

Table 1. Characteristics of patients at baseline.

A/A	Gender	Age (years)	ALT (U/l)†	HBVDNA (copies/ml)‡	HBsAg	antiHBc	HBeAg	AntiHBe
1	Male	77	71	NP	positive	positive	negative	positive
2	Male	73	N	$1x10^7$	positive	positive	positive	negative
3	Male	25	168	<400	positive	positive	negative	positive
4	Male	65	65	$2,8x10^3$	negative	positive	negative	negative
5	Male	56	N	<400	positive	positive	negative	positive
6	Male	52	N	$1,6x10^3$	positive	positive	negative	positive
7	Male	47	N	<400	positive	positive	negative	positive
8	Male	64	N	$1,1x10^3$	negative	positive	negative	negative
9	Male	62	N	$6,4x10^2$	negative	positive	negative	negative
10	Female	71	N	$1,6x10^3$	positive	positive	negative	positive

† N: normal values, ‡ NP: this test was not performed

Table 2. Hematologic malignancy and chemotherapy administered to the patients.

A/A	Hematologic malignancy	Chemotherapy prior to the administration of lamivudine †	Chemotherapy after the administration of lamivudine‡
1	NHL high grade	CHOP	CHOP, RTX
2	CLL	CHL+corticosteroids, FL, CVP	CVP, RTX, FL+MIT+corticosteroids
3	ALL	CVAD	CVAD, MTX, ASP, ARAC, AVAP, BEC, MP
4	CLL	CHL+corticosteroids	CHOP, FL+MIT+corticosteroids
5	AA	None	CSA, ATG+corticosteroids
6	NHL high grade	None	CHOP+RTX
7	MW	None	COP, RTX
8	AML	ARAC+IDA	ARAC+IDA+ETO, ARAC+MIT
9	CLL	CHL	FL+MIT+corticosteroids, PEN
10	NHL high grade	None	CHOP

† NHL: non-Hodgkin's lymphoma CLL: chronic lymphocytic leukemia ALL: acute lymphoblastic leukemia AA: aplastic anaemia MW: Waldenström's macroglobulinemia AML: acute myeloid leukemia

‡ CHOP: cyclophosphamide, adriamycine, vincristine, prednisone, CHL: chlorambucil, FL: fludarabine, CVP: cyclophosphamide, vinblastine, prednisone, CVAD: cyclophosphamide, vincristine, adriamycine, dexamethasone, ARAC: cytarabine, IDA: idarubicine, RTX: rituximab, MTX: methotrexate, ASP: asparaginase, AVAP: cytarabine, vincristine, adriamycine, prednisone, BEC: carmustine, etoposide, cyclophosphamide, prednisone, MP: mercaptopurine, CSA: cyclosporine, ATG: antithymocyte globuline, COP: cyclophosphamide, vincristine, prednisone, ETO: Etoposide, MIT: Mitoxantrone, PEN: Pentostatin

levels were 1100 copies/ml (range 640 copies/ml - 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 (three cases each). Six patients had been treated with chemotherapy prior to the initiation of lamivudine, which included corticosteroids in four of tcases. In these patients, chemotherapy had been initiated at a median of 12 months (range 1-36 months) prior to the administration of lamivudine, while the last chemotherapy regimen had been administered at a median of one month (range 0.5-3 months) before beginning lamivudine prophylaxis. All patients were treated with chemotherapy after the initiation of lamivudine, which included corticosteroids in nine cases.

Lamivudine was given per os at a dose of 100 mg, once daily, since creatinine clearance was above 50ml/min in all patients. In four patients who had not been previously treated with chemotherapy, lamivudine was started 19 days (median) (range, 0-35 days) prior to beginnign chemotherapy. The administration of lami-

vudine has not been stopped since in any of our patients.

RESULTS

Results are shown in Table 3. 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.

At last examination, nine patients had normal aminotransferase levels while HBV-DNA levels were decreased in all patients who had detectable HBV-DNA at baseline.

After a median follow-up of 15 months (range 6-38 months), acute hepatitis was observed in one patient (patient 1 in Tables 1-3). This patient, 28 days after the fourth chemotherapy cycle (CHOP), developed an asymptomatic rise of aminotransferase levels (SGOT 1365 U/l and SGPT 1200 U/l). Chemotherapy was administered in part; at this time he started to receive lamivudine. The rise of aminotransferase levels was attributed to drug toxicity; indeed, 10 days later their levels were normal. After 28 days he developed jaundice and his biochemical tests included SGOT 934 U/l, SGPT 1004 U/l, direct bilirubin 12mg/dl, ALP 261 U/l, γGT 130 U/l. AntiHBcIgM was detected at a low titer and while the HBV-DNA levels were still pending, he was considered to have HBV reactivation and started to receive ganciclovir, 5mg/Kg b.i.d. IV, along with lamivudine. After a few days, HBV-DNA levels ($1.7x10^3$ copies/ml) excluded the diagnosis of HBV-reactivation, ganciclovir was discontinued and drug toxicity was once more implicated as the cause of hepatitis. The patient continued to receive lamivudine while he was in remission and 10 months later relapse occurred with bone involvement and we was given rituximab. No further rise in aminotransferase levels was observed; the patient died of pneumonia six months later.

Another patient (patient 2 in tables 1-3), 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 $3x10^6$ IU three times a week along with lamivudine. He received combined treatment for 14 months but HBV-DNA levels exhibited only transient decrease. Therefore, interferon was discontinued and he has recently been 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 two times the upper normal limits) and transient increase throughout a follow-up time of more than three years.

Four patients demonstrated a transient, slight increase of aminotransferase levels during the treatment which was attributed to chemotherapy toxicity.

DISCUSSION

Reactivation of hepatitis B in patients with chronic HBV infection is part of the natural history of the infection and can occur spontaneously, with no apparent cause. Its annual incidence rises to 7.3% of patients and it might relapse or last for a long time (up to more than

Table 3. Results of treatment at the end of follow-up.

A/A	AST/ALT (U/l)	HBVDNA (copies/ml)	Response to chemotherapy† (months)	Follow-up
1	N	$5,4x10^2$	CR→RE→Death	16
2	N	$1.3x10^5$	PR	38+
3	81	<400	CR	30+
4	N	<400	PR	29+
5	N	<400	Death	12
6	N	<400	CR	17+
7	N	<400	PR	14+
8	N	<400	PR→RE→Death	9
9	N	<400	PR→RE→Death	12
10	N	<400	PR	6+

† CR: complete response, RE: relapse, PR: partial response

two years).[25,26] Reactivation is much more frequent in immunosuppressed patients.[27] As the number of immunosuppressed patients has been rising lately, due to HIV infection and organ transplantation, this complication is gaining more attention.[4]

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. During this period, rises in viral load and reappearance of HBeAg have been observed. 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 more than 25 years and poses a major risk for these patients, with varying morbidity and mortality rates. This variability possibly reflects the small number of patients studied.[1,2,17,28-32] The severity of the subsequent liver damage cannot be predicted and may present over a wide range, from slight elevation of aminotransferases to fatal, fulminant hepatitis.[13,20,33] Reactivation might also predispose to progression to chronic hepatitis, which hinders the completion of the chemotherapy regimen, or might lead to extensive liver necrosis and later on to cirrhosis, even in the case of cure of the hematologic malignancy.[4,8,34]

Lamivudine is a deoxycytosine analogue that directly suppresses HBV replication by incorporation of its monophosphate form into DNA by HBV polymerase. It currently represents a first-line treatment for chronic hepatitis B.[15,20,35] It is also effective in HBV carriers who are treated with cytotoxic agents.[13] It demonstrates low cytotoxicity to marrow progenitor cells, thus allowing its concomitant administration with chemotherapy and is well tolerated even in long-term therapy.[13,15-17,35]

Until recently, treatment of hepatitis B flare-up included supportive care only, while plasma exchange, corticosteroids and interferon had exhibited limited efficacy.[11] Recently, lamivudine 100-300mg daily 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. Nevertheless, in one study, despite of the administration of lamivudine 100-300mg daily two days after the flare-up, mortality was 67%.[7] One possible explanation is that even though lamivudine suppresses HBV replication, the presence of a high viral load on the liver before its administration inevitably leads to massive liver necrosis.

To date, available strategies for the prevention of HBV reactivation are few and lack effectiveness and documentation. Treatment of these patients with reduced intensity chemotherapy has been suggested, 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.[20,23,36] Interferon, with or without corticosteroid priming (which reportedly enhances its effectiveness against HBV), has been used in a few cases, but is often prematurely withdrawn because of its hematologic toxicity.[37-39] One of our patients, due to a lack to response to lamivudine, was given interferon but did not respond.

Prophylactic administration of lamivudine was implemented in only 14 patients who had non-Hodgkin's lymphoma and chronic hepatitis B and who were treated with autologous bone marrow transplantation or conventional cytotoxic agents. Lamivudine 100-300mg daily was started during chemotherapy and for 4 to 18 months after its completion, and was occasionally combined with interferon. It prevented hepatitis B flare-up without affecting peripheral blood stem cells harvesting and did not caused no modifications in the chemotherapy regimens or affected their effectiveness or hematological recovery after their completion.[13,18,20-23] In a single study, lamivudine 100mg daily was given before chemotherapy was began and for one month after its withdrawal in 20 patients with lymphoid malignancies, and it showed similar results with no adverse effects.[8] There are also two studies where lamivudine 100-300mg daily was given to 29 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]

Our study confirms the effectiveness of prophylactic administration of lamivudine in preventing hepatitis exacerbation in patients with chronic hepatitis B and who are being treated with chemotherapy for hematologic malignancies. Only one patient exhibited acute hepatitis, which was attributed to drug toxicity. Viral replication was suppressed by lamivudine and this resulted in a reduction or normalization of aminotransferase and HBV-DNA levels.

Nine out of ten patients in our study received corticosteroids as a part of the chemotherapy regimen. Corticosteroids are the most significant predisposing factor to HBV reactivation, since they promote viral replication

both directly and indirectly by causing immunosuppression.[4] HBV-DNA has been found to contain a glucocorticoid responsive element.[37] Corticosteroids specifically activate HBV gene expression in cultured human hepatoma cells transfected by HBV genomes.[38] In a comparative trial, flare-ups occurred in 47.4% compared 8.3% in HBV carriers with non-Hodgkin's lymphoma treated with corticosteroid-containing and corticosteroid-free chemotherapy respectively.[9]

Male gender is also an independent risk factor for HBV reactivation,[3,5] but even though all our patients except one were male, flare-ups did not occur. High viral load ($>10^5$ copies/ml) before chemotherapy is one of the more important predictors of hepatitis exacerbation, but our patients, in spite of their high mean viral load ($1.0x10^6$ copies/ml), did not develop acute hepatitis.[39] The majority of our patients were 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, did not lead to flare-ups, further supporting the efficacy of lamivudine in this setting.[1-11]

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

Since hepatitis flare-ups might occur as late as 90-105 days after the withdrawal of chemotherapy (this time interval is necessary for restoration of immunocompetence),[4,7] lamivudine should be given for a longer period of time and maybe indefinitely. It is also well known that HBV infection can relapse in a significant percentage (19-50%) of patients treated with lamivudine shortly after its discontinuation, leading even to acute liver failure.[7,13,20,40-42] Nevertheless, long-term administration of lamivudine is associated with a rise in resistant HBV mutants in 20% of patients after one year and even more frequently in more prolonged treatment. 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.[35] None of our patients showed evidence of a breakthrough infection despite the protracted administration of lamivudine.

Several studies have reported a higher prevalence of hepatitis B in patients with lymphoma than in the general population.[33,43] It is not certain whether HBV is involved in the pathogenesis of lymphomas or whether the immunosuppressive effect of lymphomas prohibits HBV clearance.[33] One other explanation is that both lymphoma and hepatitis B develop as independent events in patients with deficient immune systems.[43] It is therefore possible that lamivudine, will improve the response rates to chemotherapy, just as interferon does.[44,45]

During immunosuppression, HBV has been reported to be directly cytopathic and to cause a rare form of hepatitis (fibrosing cholestatic hepatitis) characterized by periportal fibrosis, ballooning degeneration of hepatocytes, prominent cholestasis and paucity of inflammation. Thus, inhibition of HBV replication by the long-term administration of lamivudine might have additional benefits.[46]

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. They should, therefore, be monitored closely or even given lamivudine.[4,13,47-49] This is the first report on the preemptive administration of lamivudine in patients with hematologic malignancies and isolated antiHBc.

Lamivudine might cause transient asymptomatic elevations of amylase, lipase and creatine phosphokinase levels in a few patients; this side effect lacks clinical significance. Generally, incidence of its adverse events was similar to that of placebo in most trials.[35] In our patient cohort, no adverse effects associated with the administration of lamivudine were observed.

Our study has a few limitations. First, a really preemptive 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 three 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 and for HBV-DNA levels. Those who are HBsAg carriers, or antiHBc positive with detectable HBV-DNA, should be given lamivudine prior to chemotherapy and for at least six months after its withdrawal. The optimal duration of treatment and the role of new nucleoside analogues, such as adefovir dipivoxil, in patients who develop resistant HBV mutants remain to be evaluated in prospective large-scale studies.

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