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Lamivudine prophylaxis in HBV carriers with haemato-oncological malignancies who receive chemotherapy

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Reactivation of hepatitis B virus (HBV) is a well-recognized complication of chemo/immunosuppressive therapy in individuals who are HBV surface antigen-positive inactive carriers and in individuals with chronic HBV infection. Although it is well established that chemo/immunosuppressive therapy enhances HBV replication with a resultant increase in the viral load and disease activation, the role of prophylactic lamivudine therapy to prevent chemo/immunosuppressive therapy-induced HBV activation in HBV-positive individuals who are to receive chemo/immunosuppressive therapy remains controversial. The aims of the present article are: (i) to determine the effect of lamivudine prophylaxis in HBV carriers with haemato-oncological malignancies who require chemotherapy; (ii) to define the duration and safety of lamivudine in such individuals; and (iii) to identify the effect of lamivudine prophylaxis on the outcome of chemotherapy administered for the primary disease. The data currently available suggest that lamivudine prophylaxis prevents chemotherapy-induced HBV reactivation in HBV carriers with haemato-oncological malignancies who receive chemotherapy. Lamivudine is safe and tolerable in such individuals. The duration of lamivudine prophylaxis is not yet known; however, it would appear prudent to begin lamivudine at the time of the initiation of the chemotherapy and to continue it throughout the period of chemotherapy administration and for at least 1 and possibly 2 years following the discontinuation of the chemotherapy. Finally, the prophylactic use of lamivudine in inactive HBV carriers with haemato-oncological malignancy prevents interruptions in their treatment for primary disease as a result of HBV reactivation.

Keywords: hepatitis B virus, 3TC, antiviral

Hepatitis B virus

Hepatitis B virus (HBV) is a small DNA virus that belongs to the family of Hepadnaviridae.[1] The World Health Organization estimates that worldwide more than 300 million people are chronic HBV carriers.[1,2] A significant proportion of these individuals develop chronic hepatitis, which is associated with an increased risk of both morbidity and mortality.[1,2]

Geographical patterns of HBV prevalence vary greatly, with areas of low endemicity (HBV carriage rate, $<2\%$) to areas of high endemicity (HBV carriage rate, $>7\%$).[2] The prevalence of HBV surface antigen (HBsAg) positivity in Turkey averages 5%, being lower in western regions (3.9%) and higher in eastern regions (12.5%) of the country.[3] The prevalence of HBsAg-positive individuals requiring haematopoietic cell transplantation has been reported to be 1% in American recipients, 3.5% in European recipients and 9% in Turkish recipients.[3–5]

HBV infection is associated with a spectrum of clinical presentations that vary as a function of age and the immunological status of the infected individuals. More than 90% of adult immunocompetent adults who become infected clear the infection, whereas disease chronicity occurs in individuals who are immunocompromised for any reason. Histologically, HBV-induced liver disease varies from a near normal liver to an aggressive chronic hepatitis, which can occur with/without cirrhosis and in some cases hepatic cancer.[1,6] HBsAg carriers with normal aminotransferases levels and normal/minimal hepatic histological changes are typically anti-HBe-positive and anti-HBc IgM negative, and have low HBV-DNA levels (in the range 10^3–10^5 copies/mL); they constitute a large proportion of the HBV-infected populations. These individuals have inactive disease characterized by prolonged phases of inactive HBV replication and apparent quiescence of their liver disease, alternating with phases of viral reactivation and exacerbation of the hepatic disease.

The primary goal of therapy for HBV infection is the sustained eradication of viral replication, the elimination of any biochemical and histological hepatitis and the prevention of subsequent HBV-related morbidity and mortality. Currently, of

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JAC antiviral

the available anti-HBV drugs, lamivudine (3TC) is the only nucleoside (cytosine) analogue that has been used widely for the treatment of HBV infection.[7] Lamivudine is a reverse-transcriptase inhibitor of viral DNA polymerase.[7] The active drug is a phosphorylated metabolite, which has potent antiviral activity against HBV.[7] Numerous studies have shown that lamivudine therapy of chronic hepatitis B results in clinical, biochemical and serological resolution of the HBV infection in immunocompetent individuals.[7,8] It is a remarkably safe drug, only rarely manifesting mild adverse effects. Unfortunately, the effectiveness of long-term lamivudine treatment decreases progressively as a result of the emergence of resistant mutant HBV strains. Emergence of lamivudine-resistant HBV is associated with viral load rebound and results in a higher rate of liver disease progression.[7]

HBV reactivation

Reactivation of HBV is a well-recognized complication of chemo/immunosuppressive therapy in both HBsAg-positive inactive carriers and in individuals with chronic HBV infection.[9,10] Reactivation of HBV infection occurs in 14–50% of such individuals, and the mortality associated with viral reactivation varies from 3.7–60%.[9,10] Yeo *et al.*[11] reported hepatitis at a rate of 44% in a large series of haemato-oncological malignancies ($n = 626$), and HBV reactivation accounted for 44% of those. A higher reactivation rate was reported in individuals with lymphoma.[11] Several factors contribute to the development of viral reactivation in HBV carriers with malignancies who are receiving chemotherapy (Table 1).[9,12–14]

HBV reactivation-related hepatitis is defined as an elevation of serum aminotransferase levels occurring in association with the demonstration of HBV replication markers (reversion of anti-HBe antibody and/or detection of anti-HBc IgM positivity). A positive serum HBV-DNA assay is required to confirm HBV reactivation. Liver biopsy is not contraindicated in individuals with underlying haemato-oncological malignancies, but the presence of severe thrombocytopenia, a concomitant haemorrhagic diathesis and highly elevated aminotransferase levels limit the application of this procedure unless performed transvenously.

Although it is well known that chemo/immunosuppressive therapy enhances viral replication,[9–12] the role of prophylactic antiviral therapy to prevent chemo/immunosuppressive therapy-induced HBV reactivation in candidates for such therapy is less established and remains controversial.

Table 1. Factors predisposing to HBV reactivation in HBV carriers who receive chemotherapy

Host-related	primary haemato-oncological disease (lymphoma[a])
	pre-existing liver disease
	young age
	male gender
Virus-related	high serum HBV-DNA levels
Treatment-related	high dose of chemotherapy
	corticosteroid treatment[a]

[a]Both lymphoma and steroid therapy predisposing to HBV reactivation in HBV carriers who receive chemotherapy are not known very well.

Lamivudine used as prophylaxis of HBV reactivation

Because the prevalence of HBV infection is high in individuals with haemato-oncological malignancies and the treatment of individuals with these malignant processes is associated with enhanced rates of viral replication, several investigators have examined the efficacy and tolerability of lamivudine therapy as a prophylactic agent preventing HBV reactivation in these individuals (Table 2).[15–18] The principal aims of these studies have been: (i) to determine the effect of lamivudine prophylaxis on the rate of HBV reactivation in inactive HBV carriers with haemato-oncological malignancies who receive chemotherapy; (ii) to define the duration and safety of lamivudine prophylaxis in these cases; and (iii) to identify the effect of lamivudine prophylaxis on the outcome of treatments given for the haemato-oncological malignancy.

We have had experience with 18 HBV carriers being considered for chemotherapy to treat a primary haemato-oncological malignancy.[18] Eight of them were administered prophylactic lamivudine at a dose of 100 mg/day at the initiation of their first cycle of chemotherapy and the remaining 10 subjects were studied as controls. The lamivudine was maintained for a full year following discontinuation of any chemotherapy. No HBV-related mortality was observed in either group during or after the administration of chemotherapy. None of the lamivudine-treated individuals showed evidence of HBV reactivation during the course of their chemotherapy treatments and for a full year after the discontinuation of chemotherapy. This result is comparable with that reported by other investigators.[15–17] Thus, prophylactic lamivudine treatment appears to prevent HBV reactivation in inactive HBV carriers with haemato-oncological malignancies who receive chemotherapy.

In contrast, 50% of the individuals in the control group demonstrated evidence of HBV reactivation. At the time of reactivation, four of these subjects were actively receiving chemotherapy. The one remaining individual had completed her course of chemotherapy at the time of reactivation. This rate of HBV reactivation in the control group is comparable with that reported in other studies (Table 2).[15–17] But in contrast to Lim *et al.*,[16] who reported a high HBV-related-mortality (26%) in HBV carriers who receive chemotherapy, no HBV-related mortality was observed in our group.[18] Based on these results, inactive HBV carriers who receive chemotherapy should be placed on lamivudine prophylaxis.

Treatment of HBV reactivation

Generally, chemotherapy-induced HBV reactivation in HBV-positive individuals with haemato-oncological malignancies receiving treatment for their disease has been managed primarily by the discontinuation of the chemotherapeutic agents and the addition of supportive care. This course of action does not stop the liver damage in most cases. In contrast, antiviral agents, either interferon or nucleoside analogues, showed variable ability to interfere with HBV replication in such individuals. Two other antiviral agents, ganciclovir and famciclovir, have moderate anti-HBV activity but have clinically important limitations, particularly myelotoxicity.[4,14,19] Unlike lamivudine, interferon has significant haematopoietic toxicity and often enhances

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Table 2. Characteristics of hepatitis B virus carriers treated with lamivudine

Author	Patients (*n*)		Lamivudine dose	HBV reactivation	Adverse effects	HBV-related mortality
	lamivudine group	control group				
Rossi *et al.*[15] 2001	20	0	100 mg/day	5% (1/20)[a]	well-tolerated	0
Lim *et al.*[16] 2002	16	19	100–300 mg/day	0 versus 37% (7/19)	well-tolerated	0 versus 26% (5/19)
Shibolet *et al.*[17] 2002	13	5	150 mg/day	0 versus 40% (2/5)	well-tolerated	0
Idilman *et al.*[18] 2004	8	10	100 mg/day	0 versus 50% (5/10)	well-tolerated	0

[a]HBV reactivation was observed after lamivudine therapy was discontinued.

the severity of clinically evident hepatitis B as a result of its action to augment immune-mediated liver damage.[14]

The effectiveness of lamivudine in the treatment of HBV reactivation in individuals with haemato-oncological malignancy has been proven in a number of reports;[14,20,21] however, low efficacy of lamivudine treatment has also been reported in a small series.[22] Responding individuals showed clinical, biochemical and serological improvement. The previous studies have shown that lamivudine treatment was life-saving in transplant recipients with HBV reactivation, whereas prognosis of recipients with HBV reactivation who did not receive lamivudine was dismal.[4,23] In our work, lamivudine was administered to all individuals with HBV reactivation, including those in the control group. On lamivudine treatment, the liver injury abnormalities characteristic of HBV reactivation fell to normal levels within 2 weeks–2 months after the initiation of lamivudine treatment. HBV-DNA became undetectable in all individuals receiving lamivudine therapy. Once the liver injury tests were normal and HBV-DNA was undetectable, the chemotherapy regimens were restarted.[18]

Duration of lamivudine therapy

The optimal duration of lamivudine prophylaxis in individuals at risk for HBV reactivation because of haemato-oncological malignancy has been investigated.[15–17] However, there are no clear data in the literature to indicate how long prophylactic lamivudine therapy should be continued in HBV carriers with haemato-oncological malignancy who will receive chemotherapy. Long-term (>1 year) antiviral therapy is required to eradicate HBV infection in immunocompetent individuals because of the high rate of HBV replication (plasma half-life of HBV, 24 h) and the relatively slow turnover rate of HBV-infected hepatocytes (half life, 10–100 days).[7,8] Lamivudine produces a rapid reduction in HBV replication within days to weeks of its initiation in immunocompetent individuals with chronic HBV infection.[7,8] In immunosuppressive subjects, several investigators have suggested that the duration of lamivudine treatment in cases with inactive HBV infection receiving chemo/immunosuppressive therapy should continue for at least 6 months following the last dose of therapy.[15,16] Shibolet *et al.*[17] treated their HBV-positive patients, who were candidates to receive immunosuppressive therapy, with lamivudine prophylaxis for a total of up to 2 years (0.5–24 months; mean 7 months) after completion of immunosuppression treatment. In our experience,[18] one of the HBV reactivations occurring in the lamivudine untreated group occurred 12 months after the individual's chemotherapy had been discontinued. Thus, long-term lamivudine prophylaxis in individuals with haemato-oncological malignancy at risk for HBV reactivation seems to be reasonable.

Side effects of lamivudine therapy

The previous studies have shown that the adverse effect profile of lamivudine is reasonable because it does not overlap with that of chemotherapeutic agents, making this agent particularly suitable for simultaneous use with chemotherapy.[14–17] No haematological abnormalities, hepatic enzyme flares or reduction in chemotherapy dosage were observed in our studies in those receiving lamivudine, as also reported by other investigators.[15–17] Therefore, careful and strict monitoring of haematological parameters of such individuals is not necessary during lamivudine therapy.

According to published data, the risk of developing lamivudine-resistant HBV increases with the duration of lamivudine treatment.[7] Most cases of resistance are associated with mutations in the YMDD motif of the polymerase gene.[7] Resistance rates between 15–40% have been reported after 2 years of lamivudine treatment in immunocompetent individuals with chronic HBV infection.[7] In immunosuppressive individuals, Chan *et al.*[23] reported a cumulative resistance rate of 41% after 31 months in HBsAg-positive kidney allograft recipients receiving lamivudine.[23] Lau *et al.*[4] reported only one allogeneic haematopoietic cell transplant (1/20) case treated with lamivudine who developed lamivudine resistance at week 40. Rossi *et al.*[15] reported that no HBV carrier with lymphoid malignancies treated with chemotherapy developed lamivudine resistance during a limited duration of lamivudine prophylaxis (1 month after completion of the chemotherapy cycles).[15] None of the individuals we studied with haematological malignancy who received lamivudine has developed a lamivudine-resistant virus after a mean of 14 months of continuous lamivudine therapy.

The development of HBV resistance has been a factor limiting the durability of the therapeutic effectiveness of lamivudine treatment. Adefovir dipivoxil, a monophosphate nucleotide analogue, was approved by the United States Food and Drug Administration and represents the newest approach to the treatment of HBV infection.[24] In contrast to lamivudine, there is lack of viral resistance with prolonged therapy with adefovir dipivoxil in immunocompetent individuals.[24] Moreover, adefovir is effective against the HBV mutant virus. There are no data available concerning the efficacy, safety and tolerability of adefovir

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dipivoxil when used to treat lamivudine-resistant HBV reactivation in individuals with haemato-oncological malignancies. Additional studies are needed to clarify the role of adefovir dipivoxil in immunosuppressed individuals, to define its efficacy and to identify any adverse haematological side effects.

Current status of lamivudine therapy

Not only did lamivudine prevent viral reactivation in individuals with haemato-oncological malignancy receiving chemotherapy, it also allowed all of them to complete their chemotherapy regimens without interruption.[15–18] In contrast, 50% of the subjects in the control group had to discontinue their chemotherapy regimen for a mean of 3.0 months as a result of an episode of HBV reactivation.[18]

In conclusion

The data currently available suggest that:

i) lamivudine prophylaxis in inactive HBV carriers with haemato-oncological malignancies who receive chemotherapy prevents chemotherapy-induced HBV reactivation;

ii) lamivudine is effective, safe and tolerable in such individuals;

iii) a daily oral dose of 100 mg of lamivudine appears to be sufficient to prevent flares of HBV reactivation as a result of chemotherapy;

iv) the ideal protocol of lamivudine prophylaxis for the prevention of HBV reactivation in individuals receiving chemotherapy for haemato-oncological malignancies is not yet known. However, it would appear prudent to begin lamivudine at the time of the initiation of the chemotherapy, and to continue it throughout the period of chemotherapy administration and for at least 1 but possibly 2 years following the discontinuation of the chemotherapy;

v) finally, the prophylactic use of lamivudine in inactive HBV carriers with haemato-oncological malignancy prevents interruptions of their treatment as a result of HBV reactivation.

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