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Lamivudine in the Treatment of Hepatitis B Virus Reactivation During Cytotoxic Chemotherapy

Winnie Yeo,[1]* Joyce L. Steinberg,[1] John S. Tam,[2] Paul K.S. Chan,[2] Nancy W.Y. Leung,[3] Kwok C. Lam,[1] Tony S.K. Mok,[1] and Philip J. Johnson[1]

[1]*Department of Clinical Oncology, Chinese University of Hong Kong, Sir YK Pao Cancer Centre, Prince of Wales Hospital, Shatin, NT, Hong Kong*
[2]*Department of Microbiology, Chinese University of Hong Kong, Sir YK Pao Cancer Centre, Prince of Wales Hospital, Shatin, NT, Hong Kong*
[3]*Department of Medicine, Chinese University of Hong Kong, Sir YK Pao Cancer Centre, Prince of Wales Hospital, Shatin, NT, Hong Kong*

Hepatitis B virus (HBV) reactivation has been described in cancer patients who received cytotoxic/immunosuppressive therapy and may result in liver damage of varying degrees of severity. There is no known effective treatment. Lamivudine, a nucleoside analogue, has been found to suppress HBV replication and to improve histology in chronic carriers of hepatitis B virus. The outcome of lamivudine therapy (at doses of 100 or 150 mg/day) in eight patients who developed HBV reactivation while receiving cytotoxic chemotherapy is described. Each of the eight patients had >98% suppression of the pretreatment HBV DNA levels. Three of the five patients who were initially HBeAg positive underwent seroconversion. Five patients had normalization of liver function tests and improvement in clinical condition. However, one patient died of hepatic failure due to HBV-related submassive liver necrosis, and two died of widespread metastases (including liver) from the primary malignancies. It is concluded that early commencement, i.e., at the onset of HBV reactivation before severe hepatic decompensation, of lamivudine may be effective in the control of HBV reactivation during chemotherapy. In Hong Kong, where hepatitis B infection is endemic, we propose to screen all cancer patients for hepatitis B surface antigen before immunosuppressive/cytotoxic therapy, and to closely monitor liver function of those who are found to be HBsAg seropositive. ***J. Med. Virol. 59:263–269, 1999.*** © 1999 Wiley-Liss, Inc.

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INTRODUCTION

Chronic infection with hepatitis B virus (HBV) affects about 5% of the world's population [Kane, 1993]. Until recently, interferon had been the only approved treatment. However, several other specific therapies are being developed. Currently, the nucleoside analogues are the most promising agents [Fontana and Lok, 1997], and lamivudine has recently been approved in several countries for the treatment of chronic HBV infection. HBV reactivation has been well described in patients with cancer who received cytotoxic therapy. Most reports concerned hematological malignancies [Galbraith et al., 1975; Hoofnagle et al., 1982; Lau et al., 1989; Liang et al., 1990; Lok et al., 1991; Pinto et al., 1990; Soh et al., 1992; Thung et al., 1885; Wong et al., 1996]. Reactivation in patients with other tumors is much less common [Galbraith et al., 1975; Hoofnagle et al., 1982]. In contrast with exacerbation of chronic HBV infection, HBV reactivation occurs after a patient has been started on immunosuppressive therapy. There is more active viral replication as reflected by a high level of HBV DNA. HBV reactivation may result in varying degrees of liver damage, ranging from anicteric hepatitis to fatal liver failure [Liang et al., 1990]. There has been no effective treatment for patients suffering from this condition; the availability of an antiviral agent such as lamivudine offers therapy for these patients. Eight patients who developed hepatitis B viral reactivation during chemotherapy and their responses to the use of lamivudine are described.

PATIENTS AND METHODS

Eight patients were diagnosed with cancer and underwent combination chemotherapy. There were seven males and one female. The median age was 50 years (range: 20–64). Alanine transaminase (ALT) and total

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*Correspondence to: Winnie Yeo, Department of Clinical Oncology, Sir YK Pao Cancer Centre, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong.

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bilirubin levels were normal in all patients before chemotherapy. The patients' characteristics are summarized in Table I.

Five of the eight patients were known to be hepatitis B surface antigen (HBsAg) carriers before the start of chemotherapy, they were followed up regularly during the course of chemotherapy. At the first signs of hepatic dysfunction (defined by a rise in ALT ± total bilirubin), they were asymptomatic. The remaining three patients complained of lethargy during chemotherapy and were then noticed to have impaired liver function, at which time they were found to be HBsAg positive and IgM antibody to the hepatitis B core antigen (IgM anti-HBc) negative. Among the eight patients, five were HBeAg positive, and the other three who were HBeAg negative were subsequently found to have mutations of HBV pre-core and pre-core promoter regions. Screening tests for Epstein-Barr virus (EBV), cytomegalovirus (CMV), and hepatitis A, C, and delta viruses were negative in all patients. HBV DNA level was measured by the branched DNA hybridization assay (Chiron, USA). The median HBV DNA level was $4{,}582 \times 10^6$ Eq/ml, with a range of 2,190 to $>4{,}900 \times 10^6$ Eq/ml (median: 16,365 pg/ml, range: 7,821 to >17,500 pg/ml). On the basis of clinical features and the above investigations, all eight patients were diagnosed with HBV reactivation.

The chemotherapeutic agents used are illustrated in Table I. The median number of cycles of chemotherapy the patients received before HBV reactivation was 3 (range: 1–4). The median time from the start of chemotherapy to time at which reactivation occurred was 65 days (range: 8–122).

At the time of HBV reactivation, ultrasonography of the patients showed that four had normal hepatic echotexture, one had evidence of hepatitis, one had cirrhosis with portal hypertension, and two had persistent liver metastases despite chemotherapy.

Lamivudine was commenced at a daily dose of 100 mg for patient 1 and 150 mg for the other seven patients. Table II illustrates the liver function tests of each patient at commencement of lamivudine. All patients had raised ALT with a range of 124–2280 IU/L (normal: <58), in particular, the ALT levels of patients 1 and 6 were 10 times over the upper normal limit. With respect to total bilirubin level, it was mildly raised in patients 2, 3, 4, 5, and 8 and ranged between 3–30 μmol/l (normal: <5), moderately elevated in patient 7 at 93 μmol/L, and grossly raised in patients 1 and 6 at levels of 140–316 μmol/L (i.e., close to or above 10 times the upper normal limit). Albumin levels varied at 21–37 g/L. The prothrombin time of the patients was within the range of 11–23 sec and, in particular, that of patients 1 and 6 was prolonged for over 5 sec. Patients 1, 6, and 7 were only known to be HBsAg carriers after they had developed severe liver dysfunction, therefore the delay in the diagnosis of HBV reactivation had led to the subsequent delay in the administration of lamivudine.

RESULTS

Apart from patient 5, who continued to receive the same chemotherapeutic regime whilst on lamivudine, chemotherapy was discontinued in the other seven patients. The results are illustrated in Table II. The liver function of patients 2, 3, 4, 5, and 6 improved with the commencement of lamivudine. However, that of patients 1, 7, and 8 continued to deteriorate despite lamivudine therapy.

Virologic Outcome

All patients had >98% suppression of the pretreatment HBV DNA levels. The HBV DNA levels of seven patients (all but patient 5) fell and became undetectable, i.e., $<0.7 \times 10^6$ Eq/ml (<2.5 pg/ml) at a median time of 27 days from the start of lamivudine (range: 6–49 days). For patient 5, his HBV DNA level reduced to 10×10^6 Eq/ml (35 pg/ml) after 49 days of lamivudine therapy, rising to 55×10^6 Eq/ml (196 pg/ml) on day 79, but has since reduced to the lowest level of 1.685×10^6 Eq/ml (6 pg/ml) on day 203. All patients had persistent HBsAg throughout the duration of lamivudine therapy. However, of the five patients who were positive for HBeAg before commencing lamivudine, patients 2, 3, and 4 seroconverted (loss of HBeAg and the development of antibody to HBeAg) after 49, 63, and 87 days of starting treatment, respectively. On the basis of undetectable HBV DNA, HBeAg seroconversion, and normalization of liver function, lamivudine has been discontinued in these three patients. To date, they continue to have sustained HBV DNA suppression and anti-HBe at 11, 6, and 3 months, respectively after the discontinuation of lamivudine. One patient (patient 5) is still under treatment with lamivudine.

Clinical Outcome

Four (patients 2, 3, 4, and 6) are alive and well. They were not given further chemotherapy. There have been no signs of HBV reactivation or disease relapse from the primary malignancy. One (patient 5) continued to receive lamivudine with chemotherapy. The lymphoma responded initially to chemotherapy, but this progressed after six cycles, and as a result, he has been offered second-line chemotherapy. Three patients died: one (patient 1) from HBV-related hepatic failure despite objective response of metastatic breast cancer to chemotherapy, and two (patients 7 and 8) of disease progression from the primary malignancy. The latter was evident by increased tumor size on clinical and radiological assessments.

DISCUSSION

Two possible mechanisms have been considered responsible for HBV reactivation during chemotherapy. 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 cyto-

TABLE I. Patients' Background Characteristics

Patients	Age/sex	Primary malignancies	HBsAg	HBeAg	HBVDNA levels at diagnosis of HBV reactivation in $\times 10^6$ Eq/ml (pg/ml)	Presence of other hepatitis viruses at time of reactivation[d]	Chemotherapy regimens	No. of chemotherapy cycles before HBV reactivation	Time from start of chemotherapy to HBV reactivation in days	Finding of US liver at time of HBV reactivation
1	60/F	Breast cancer	+[b]	–[c]	>4,900 (>17,500)	–	Adr/Ctx	4	101	No abnormality
2	57/M	Lung cancer	+[a]	+	4,800 (17,143)	–	Gem/VP16	4	101	No abnormality
3	49/M	Carcinoma of renal pelvis	+[a]	+	2,444 (8,726)	–	Mtx/Vbl/Adr/Ctx	2	30	Cirrhosis with portal hypertension
4	45/M	Non-Hodgkin's lymphoma	+[a]	+	2,961 (10,575)	–	Adr/Ctx/Vcr/Pred	3	44	No abnormality
5	36/M	Non-Hodgkin's lymphoma	+[a]	+	4,364 (15,586)	–	Adr/Ctx/Vcr/Pred	1	8	No abnormality
6	20/M	Germ cell tumor	+[b]	–[c]	2,190 (7,821)	–	Carb/VP16/Ctx	2	122	Hepatitis
7	51/M	Lung cancer	+[b]	–[c]	>4,900 (>17,500)	–	Ctx/Adr/Vcr	3	118	Multiple liver metastases
8	64/M	Non-Hodgkin's lymphoma	+[a]	+	>4,900 (>17,500)	–	Adr/Ctx/Vcr/Pred	3	65	Multiple liver metastases

Adr, Adriamycin; Ctx, cyclophosphamide; Pred, prednisone; Vcr, vincristine; Vbl, vinblastine; Carb, carboplatin; VP16, etoposide; Gem, gemcitabine.
[a]Known HBsAg status before chemotherapy.
[b]HBsAg positive, IgM antibody to the hepatitis B core antigen (IgM anti-HBc) negative at the time of reactivation.
[c]Mutations of HBV pre-C and pre-C promoter regions present.
[d]Hepatitis viruses screening include Epstein-Barr virus, cytomegalovirus, hepatitis A and C, and delta viruses.

TABLE II. Details and Outcome of Patients With Lamivudine Therapy

Patients	HBVDNA levels at diagnosis of HBV reactivation in $\times 10^6$ mEq/ml (pg/ml)	Liver function at the start of lamivudine ALT/Tbili/Alb/PT[a]	Daily dose of lamivudine (mg)	Duration of lamivudine therapy (days)	Time for HBVDNA to fall to undetectable state (days)	HBsAg/ HBeAg status	Latest liver function prior to discontinuation of lamivudine*/ while on lamivudine**/ at time of death*** ALT/Tbili/Alb/PT	Outcome	Survival (from the time of diagnosing of reactivation) (days)
1	>4,900 (>17,500)	603/140/21/21	100	40	14	No change	64/165/18/19***	Died of HBV reactivation	48
2	4,800 (17,143)	289/30/28/14	150	107	38	Seroconversion at 49 days	37/28/11/17*	Alive and well	381+
3	2,444 (8,726)	395/12/32/11	150	104	6	Seroconversion at 63 days	61/15/35/11*	Alive and well	321+
4	2,961 (10,575)	155/3/37/11	150	127	21	Seroconversion at 87 days	47/5/35/11*	Alive and well	167+
5	4,364 (15,586)	124/3/22/11	150	157	203[b]	No change	32/6/30/11**	Alive and well	197+
6	2,190 (7,821)	2280/316/35/23	150	195+	7	No change	43/32/28/11**	Alive with lymphoma	195+
7	>4,900 (>17,500)	518/93/26/14	150	58	49	No change	128/144/25/27***	Died of liver metastasis	59
8	>4,900 (>17,500)	239/26/29/13	150	32	27	No change	216/354/16/45***	Died of liver metastasis	33

[a]ALT = alanine transaminase (normal: <58 IU/L); Tbili = total bilirubin (normal: <15 μmol/L); Alb = albumin (normal: 36–48 g/L); PT = prothrombin time (sec).
[b]HBV-DNA level reduced to 10×10^6 Eq/ml (36 pg/ml) at day 49, but rose to 55×10^6 Eq/ml (200 pg/ml) on day 79, and has then reduced to the lowest level of 1.685×10^6 Eq/ml (6 pg/ml) on day 203.

toxic/immunosuppressive agents suppress normal immunological response to viral antigens and permit widespread infection of hepatocytes; with the subsequent withdrawal of cytotoxic therapy, a rebound immune response then results in hepatocyte destruction [Alexander et al., 1983; Borg et al., 1998; Galbraith et al., 1975; Hanson et al., 1986; Mondelli et al., 1982].

In the present report, the clinical courses, with the onset of hepatitis shortly after starting cytotoxic chemotherapy in five patients known to be HBsAg carriers, were consistent with HBV reactivation. For the remaining three patients, the presence of HBsAg, with very high levels of HBV DNA, in the absence of IgM anti-HBc and with negative serology for other hepatitis viruses, support the diagnosis of HBV reactivation.

Treatment advocated for HBV reactivation has included aggressive supportive therapy, use of continuous low-dose steroids, and gradual tailing off immunosuppressive cytotoxic agents, all of which aim at suppressing the immune system [Lau et al., 1991]. However, such treatments have not been found to be universally effective [Wong et al., 1996]. Interferon, which has both antiviral and immunomodulatory functions, has been used in the treatment of chronic active hepatitis due to HBV infection [Perillo, 1990; Perillo et al., 1990], but the possibility of fatal hepatitic flare during treatment has limited its use.

Lamivudine, a nucleoside analogue, has been shown to have substantial in vivo and in vitro activity against HBV [Dienstag et al., 1995; Doong et al., 1993] with significant inhibition of β and γ HBV DNA polymerase [Chang et al., 1992]. In human immunodeficiency virus (HIV) patients, HBV DNA levels have been found to be undetectable by polymerase chain reaction in 86% of HBV carriers 2 months after the commencement of lamivudine therapy [Benhanmou et al., 1996]. This rate of inhibition was higher than that reported with the use of interferon, and lamivudine has proved effective in patients who did not respond to interferon [Benhanmou et al., 1996; Schalm et al., 1995]. At daily doses of 25–600 mg, lamivudine was effective in HBV DNA suppression, and this was noted from as early as 2 weeks from the initiation of therapy [Dienstag et al., 1995]. At 1 year after lamivudine therapy for chronic HBV infection, up to 16% of the treated patients had HBeAg seroconversion and undetectable levels of HBV DNA [Lai et al., 1998]. Other trials have had similar results, with improvement in liver function and clearance of HBV DNA in up to 96% of patients in the treated group by the end of treatment [Benhanmou et al., 1996; Dienstag et al., 1995; Eron et al., 1995; Lai et al., 1997, 1998; Nevens et al., 1997].

In this study, although the administration of lamivudine resulted in the suppression of HBV replication in all patients (as evidenced by HBV DNA suppression), the decrease in ALT levels in the presence of clinical deterioration in patient 1 suggests submassive hepatitic necrosis. In patients 2, 3, 4, 5, and 6, the suppression of HBV DNA was accompanied by normalization of liver function that resulted in clinical improvement. Patient 5 did not achieve complete suppression of HBV replication. This is more likely to be attributable to the continuation of chemotherapy, which may enhance viral replication, rather than the emergence of mutant virus resistant to lamivudine [Fontana and Lok, 1997; Atkins et al., 1998]. However, in patients 7 and 8, a similar virologic response was achieved, but their liver function continued to deteriorate, attributed to progressive liver metastases.

In previous studies demonstrating the efficacy of treatment of chronic HBV carriers with lamivudine, entry to clinical trials was limited to those with only modest hepatic impairment without signs of hepatic decompensation [Benhanmou et al., 1996; Dienstag et al., 1995; Lai et al., 1997, 1998; Nevens et al., 1997]. The fact that patient 1 had continuing deterioration of liver function despite virologic response to lamivudine therapy may be related to the late stage in the disease at which lamivudine therapy was commenced. At the start of treatment, patient 1 already had severe hepatic impairment, as reflected by grossly elevated bilirubin and ALT levels; it appears that massive hepatic damage had already been established with insufficient regenerative compensation when lamivudine therapy was initiated. This is in contrast to that of patients 2, 3, 4, and 5, in whom the liver impairment was modest with bilirubinaemia of less than twice the upper normal limit and a moderately raised ALT.

Of particular interest is patient 6, whose hepatic impairment was even more severe than that in patient 1, but who responded to lamivudine and continues to improve from the reactivation episode. This might have been due to a number of contributing factors. First, patient 6 was young and his hepatic reserve was good as indicated by an albumin level of 35 g/L at the time of HBV reactivation when lamivudine was started. This in contrast to patient 1, who was 60 years old and at the corresponding time-point had an albumin level of 21 g/L. Second, when comparing the HBV DNA levels at the time of reactivation, the initial viral load in patient 1 (as reflected by HBV DNA level of >17,500 pg/ml) was much higher than that of patient 6 (7,821 pg/ml). Third, at HBV reactivation, patient 6 had no evidence of residual disease from his germ cell tumor, while patient 1 had widespread disease from her breast cancer. Although the dose of lamivudine used in patient 1 was lower than that in the other patients (100 mg compared with 150 mg/day), it may not explain the differences in the clinical outcome, as the fall in HBV DNA levels in all cases indicates adequate viral suppression with lamivudine and previous report has shown that doses of ≥100 mg/day offered similar efficacy [Dienstag et al., 1995; Lai et al., 1997; Lai et al., 1998; Nevens et al., 1997]. Interestingly, both patients 1 and 6 were found to have an HBV mutant at the precore and precore promoter regions, and the efficacy demonstrated with lamivudine in patient 6 suggests the potential use of the drug for the treatment of patients with similar conditions [Tassopoulas et al., 1998].

On the basis of the patients described in this report, it appears that early commencement of lamivudine, i.e. at the first instance when HBV reactivation is suspected during chemotherapy and before severe hepatic dysfunction, is effective. In two recent case reports, lamivudine was used in HBV reactivation during cytotoxic treatments when the patients were immunosuppressed [Borg et al., 1998; Clark et al., 1998]. For these two patients, HBV DNA levels became undetectable after 12 and 18 weeks respectively, with improvement of their symptoms and liver functions, although one patient eventually died of progressive malignant disease. In another group of immunosuppressed patients in whom recurrent or de novo HBV infection occurred after renal and liver transplantation, lamivudine has been used either as a single agent or in conjunction with hepatitis B immunoglobulin [Andreone et al., 1998; Jung et al., 1998; Markowitz et al., 1998].

It should be noted that the natural history of HBV reactivation has not been well defined, and in many instances, it apparently subsides spontaneously [Lok et al., 1991]. A randomized controlled trial is needed to study the efficacy of lamivudine in HBV reactivation during chemotherapy. However, even in regions of the world such as Hong Kong, where the HBV carriage rate is high, HBV reactivation with liver failure during chemotherapy remains a relatively uncommon clinical problem; thus, such trial has logistic difficulties especially with patient number and entry criteria. Nonetheless, even with very high HBV DNA levels and serious hepatic dysfunction, the use of lamivudine in our patients did demonstrate therapeutic potential and this appears to result in a sustained response with HBeAg seroconversion and undetectable serum HBV DNA for at least 3 months in three patients after the discontinuation of therapy.

It remains controversial as to whether earlier administration of lamivudine, i.e., prophylactic use before or at the start of any chemotherapy is warranted. In our patient population, in which hepatitis B infection is endemic, we propose to screen all cancer patients for hepatitis B antigen before immunosuppressive/cytotoxic therapy, and to have close monitoring of liver function for those who are found to be HBsAg seropositive. Based on the findings of this study, early lamivudine treatment in those with hepatitis B reactivation during chemotherapy may prevent a fatal outcome.

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