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REVIEW ARTICLE

Hepatitis B reactivation after chemotherapy: two decades of clinical research

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Abstract Hepatitis due to hepatitis B virus reactivation after cytotoxic or immunosuppressive therapy is a serious cause of liver-related morbidity and mortality. With the characterization of the underlying pathogenesis, much progress in the management of this important clinical problem has been made in the past 2 decades. By year 2008, it is mandatory to screen for hepatitis B surface antigen status before initiating intensive chemotherapy or immunosuppressive therapy. All those who are hepatitis B surface antigen positive should be started on preemptive nucleos(t)ide analogues. However, there remains important issues, such as the type and duration of nucleos(t)ide analogue therapy, which need to be understood. As not all hepatitis B surface antigen-positive patients will suffer from HBV reactivation, it is therefore useful to identify risk factors related to HBV reactivation so that patients will not be treated unnecessarily with nucleos(t)ide analogues. To date, a high baseline level of viral replication, as reflected by high serum HBV DNA level, positive serum hepatitis B e antigen, and a high intrahepatic covalently closed circular DNA level, is the most important predictor for HBV reactivation. Recently, there has been an increased awareness of reactivation of occult hepatitis B virus, especially in hepatitis B virus endemic area, such as the Asia-Pacific region. Careful epidemiological study will be needed to clarify the impact of occult hepatitis B infection in patients treated with cytotoxic or immunosuppressive therapy.

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How important is the problem?

Over the past 20 years of clinical practice at Queen Mary Hospital, we have seen a lot of progress in the management of hepatitis due to HBV reactivation in hepatitis B surface antigen carriers [1–5]. In the past, we saw patients who died of fulminant hepatic failure after being administered a few courses of cytotoxic therapy to treat their life-threatening lymphoma [6–9] and breast cancer [10–12] if they were also hepatitis B surface antigen positive. At that time, the literature report of this important clinical issue was scanty. The first report in the field was published by Wand et al. [13] who studied the effects of antitumor chemotherapeutic agents on hepatitis antigen (HBAg) and antibody (HBAb) in 25 patients with myeloproliferative and in 60 patients with lymphoproliferative disorders. This elegant study was performed at the time when only antigen and antibody associated with viral hepatitis could be semiquantified [14]. In those patients who had HBAg at the time of initiation of chemotherapy, bone marrow suppression by chemotherapeutic agents was associated with a marked increase in HBAg titer, which was then followed by hepatocellular damage, as manifested by an elevation in serum transaminase enzymes [13]. Since then, this important observation was further confirmed in other studies [8, 15, 16], with the rate of HBV reactivation ranging from 19% to 48%. Among them, one-quarter to half would be complicated, with severe hepatitis, hepatic failure, and even death [1–6, 17–20].

With the numerous clinical research performed in the past 20 years, hepatitis due to reactivation of HBV is now a

well-recognized complication in patients with chronic HBV infection receiving cytotoxic or immunosuppressive therapy. This is particularly a problem in Asia owing to the high hepatitis B surface antigen carrier rate, compounded by the recent increase in use of cytotoxic or immunosuppressive therapy for the treatment of a wide variety of clinical diseases [21]. With the increasing prevalence of HIV infection, HBV reactivation has also been observed in HBV-infected subjects with advanced immune deficiency due to HIV infection [22–27]. Hepatitis due to HBV reactivation has not only been reported in HBsAg-positive patients, HBeAg-positive [6, 28–30] or HBeAg-negative [31–41] subjects who were treated with chemotherapy and transplantation but also in HBsAg-negative patients who had past HBV infection (hepatitis B surface antibody; anti-HBs positive and hepatitis B core antibody; anti-HBc positive) [42–49], especially those treated with rituximab or alemtuzumab-containing chemotherapy [50–55].

Chemotherapy or immunosuppressive therapy related to HBV reactivation

The most commonly reported types of chemotherapy related to HBV reactivation are those used for the treatment of hematological malignancy, such as acute leukemia, myeloproliferative disorders, lymphoproliferative disorders, and plasma cell dyscrasias [5, 6, 8, 13]. Almost all these patients had intense marrow suppression with a drastic reduction of white cell count, and the rebound of the white cell with immune recovery correlates with the initiation of liver damages [56]. Severe hepatitis due to HBV reactivation has also been reported in HBV-infected patients treated with chemotherapy for other malignancies such as breast cancer [10–12], hepatocellular carcinoma [18, 57, 58], small-cell lung cancer [59], and nasopharyngeal cancer [60]. The relative lack of report in other type of malignancy is probably related to their lower incidence in HBV endemic area, such as the Asia-Pacific region. In the transplant setting, such as bone marrow transplant [1–3, 19, 20, 61], heart transplant [62], and kidney transplant [63, 64], the use of immunosuppressive therapy is mandatory to prevent graft rejection and HBV reactivation has been well characterized. Recently, the advance in therapies based on mechanisms that target critical molecular pathways of tumors has evoked considerable interest and among them, rituximab (anti-CD20) [50–54], alemtuzumab (anti-CD52) [55], infliximab (anti-TNF) [65], have been associated with HBV reactivation in HBsAg-positive as well as HBsAg-negative patients. These agents cause profound and long-lasting immunosuppression, which may account for the risk of HBV reactivation following treatment. Also, immunosuppressive agents increase HBV replication and antigen expression. As the host immune response to the virus plays a pivotal role in controlling HBV infection [66, 67], suppression of such immune responses would increase viral replication. On the other hand, immunosuppressive agents may have a more direct stimulatory effect on viral replication. Exceptionally, one immunosuppressive agent, mycophenolate mofetil (MMF), has been shown to suppress the expression of HBsAg and HBeAg as well as the replication of HBV DNA in the 2.2.15 cell in a dose-dependent manner [68, 69]. In the transplant setting, steroids, azathioprine, cyclosporine, and tacrolimus (FK 506) are commonly used to prevent graft rejection. In vitro, corticosteroid increases HBV DNA and RNA production by stimulating HBV transcription [70, 71], by binding to the glucocorticoid responsive element (GRE), and augmenting the HBV enhancer I. In addition, the use of rituximab can effectively remove or suppress anti-HBs producing B cells and cause reactivation of HBV even in HBV immune patients. This may account for the enhanced risk of rituximab-containing chemotherapy regimen in causing HBV reactivation [54].

Pathogenesis and diagnosis of HBV reactivation

With careful prospective serial serological testing, it is now known that the liver damage due to HBV reactivation is a 2-stage process. Initially, during intense cytotoxic or immunosuppressive therapy, there is a markedly enhanced viral replication, as reflected by increases in serum levels of HBV DNA, hepatitis B e antigen (HBeAg), and HBV DNA polymerase, resulting in widespread infection of hepatocytes. With the subsequent restoration of immune function due to the withdrawal of cytotoxic or immunosuppressive therapy, there is a rapid immune-mediated destruction of HBV-infected hepatocytes, which is manifested clinically as hepatitis, hepatic failure, and even death (Fig. 1) [1–5].

Based on the understanding of the pathogenesis, HBV reactivation is best defined as an increase of HBV viral replication from a low to high replicative level in patients with chronic or past HBV infection. The key issue is the demonstration of increased HBV replication in patients with serological evidence of chronic or past HBV infection. First, serological evidence of HBV reactivation, such as anti-HBe positive or HBeAg negative to HBeAg positive, and anti-HBs positive to HBsAg positive, should be obtained. However, HBsAg-positive patients could suffer from reactivation even if they remain HBeAg negative. Sequence analysis of the HBV isolated from these patients had demonstrated the presence of point mutation in the precore region that inhibited the synthesis of HBeAg [59, 72–74]. Therefore, it would be more reliable to

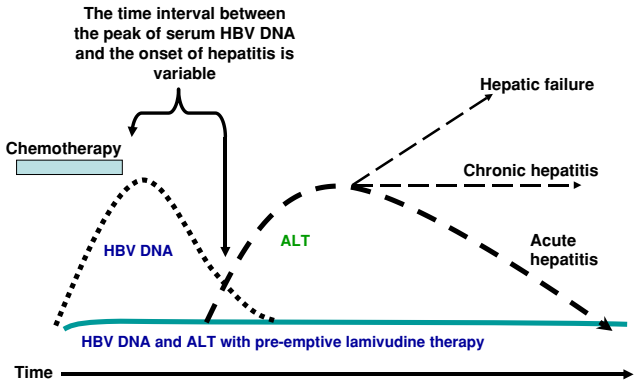

Fig. 1 Hepatitis due to HBV reactivation is a 2-phase process. The initial phase is related to intense immunosuppression caused by the cytotoxic therapy and is characterized by an enhanced HBV viral replication. There is a marked increase in serum HBV DNA level and viral protein expression in the hepatocytes. The second phase occurs during immune restoration on withdrawal of the chemotherapy and is marked by a much enhanced host immune response against HBV-laden hepatocytes, resulting in liver damages of varying severity, from hepatitis to hepatic failure and even death (solid line). The use of nucleoside analogues with anti-HBV activity in the initial phase could effectively prevent viral replication enhancement and therefore reduce the incidence of HBV-related hepatitis (dotted line)

demonstrate the presence of HBV reactivation by showing an increase of serum HBV DNA by quantitation. At the moment, the most reliable and easily performed test is the quantitation of serum HBV DNA and to track the temporal relationship of the rise in HBV DNA titers with hepatitis and chemotherapy administration [1–5, 54]. However, owing to the wide variation of the sensitivity and linearity of the different assay, the reported incidence varies. For example, the earlier branched DNA hybridization assay (Quantiplex HBV DNA assay; Chiron, Berkeley, CA) has a detection limit of 0.7×10^6 copies/ml [20], whereas recent real-time polymerase chain reaction assays have a lower detection limit down to 11 copies/ml [75]. Second, the patient should have serological evidence of chronic HBV infection. In other words, they should be HBsAg positive, preferably for at least 6 months, before HBV reactivation. In practice, this might be difficult if testing of HBV markers is not a routine before the institution of cytotoxic or immunosuppressive therapy. This is particularly the case if the patient is taking herbs, which might contain immunosuppressive elements, such as steroids, and is seen by alternate medical professionals. HBV reactivation had also been reported in HBsAg-negative patients but had serological evidence of past infection (anti-HBc positive) after immunosuppressive therapy. In HBsAg-negative patients strongly suspected to have HBV reactivation, testing of HBsAg just by monoclonal antibody-based ELISA might not be adequate as mutation in the major neutralizing epitope cluster might render a false-negative result with these assays [76]. In these instances, polyclonal assay and testing of HBV DNA should be performed [77]. Other serological tests, such as serum IgM antibody to hepatitis B core antigen (anti-HBc), are not specific enough to differentiate between acute HBV infection and HBV reactivation in patients with chronic HBV infection [78–80].

Hepatitis should be defined to be due to HBV reactivation if it was preceded or accompanied by enhanced HBV viral replication. The time interval between the peak of HBV DNA viral load and the onset of hepatitis is variable (Fig. 1) [1–5]. In the setting of allogeneic bone marrow transplantation, other causes of liver derangement, such as venoocclusive disease (VOD), GVHD, organ rejection, or superinfection with cytomegalovirus or herpes simplex virus, should be excluded [81, 82]. Because the hepatitis is preceded or accompanied by HBV virological reactivation, its diagnosis relied heavily on the serial quantification of serum HBV viral load. In our center, hepatitis was defined as a more than 3-fold increase of serum ALT on 2 consecutive determinations at least 5 days apart. Icteric hepatitis was defined as hepatitis associated with clinical jaundice and a serum bilirubin level that exceeded 30 μmol/l. HBV reactivation is defined as an increase of serum HBV DNA to more than 1 log higher than that of the preexacerbation baseline or the serum HBV DNA turned from negative to positive [1–3, 19, 20, 54, 56, 83–88]. Histological evidence of the reappearance or enhancement of active necroinflammation was not obtained in our patients because most of them had thrombocytopenia, for which percutaneous liver biopsy carried an increased risk. Moreover, from our previous experience, hepatic histological proof of reappearance or enhancement of active necroinflammation (obtained by transjugular liver biopsy) is not necessary if there is a more than 3-fold increase of serum ALT on 2 consecutive determinations at least 5 days apart, in the absence of clinical features suggestive of infection by cytomegalovirus or herpes simplex virus. In addition, hepatic failure was defined as the presence of hepatic encephalopathy and deranged blood coagulation (prothrombin time prolonged for $\geq$10 s).

Risk factors involved in HBV reactivation

Not all HBsAg-positive patients treated with cytotoxic chemotherapy or immunosuppressive therapy will suffer from HBV reactivation. Even in the setting of bone marrow transplantation (BMT), only half of the patients will suffer from hepatitis due to HBV reactivation. Moreover, for those who were treated with cyclic cytotoxic chemotherapy, HBV reactivation usually will not occur until the second or third course of therapy [6, 56]. At present, it is not at all clear what is the viral and host determinant factors to explain who will suffer from HBV reactivation.

Clinically, a good understanding of the risk factors associated with HBV reactivation in HBsAg-positive patients treated with intense cytotoxic or immunosuppressive therapy, is of paramount importance. This would give us guidance as when to use preemptive nucleos(t)ide analogue therapy and also help to elucidate the complex virus–host balance in causing HBV-related hepatic necroinflammation. Despite its clinical importance, data on the risk factors for HBV reactivation after chemotherapy are limited. As hepatitis due to HBV reactivation is preceded by enhanced HBV viral replication [1–5], a high prechemotherapy HBV viral load has been consistently found to be the most important risk factor for postchemotherapy HBV reactivation, by multivariate analysis (Table 1). In our center, by studying 137 consecutive autologous BMT patients, we first described that pre-BMT HBV DNA level $>10^5$ copies/ml (by Digene Hybrid Capture II assay) was the only significant risk factor [20] associated with post-BMT HBV reactivation. Subsequently, in breast cancer patients receiving standard cytotoxic chemotherapy, a high HBV viral load prior to the administration of cytotoxic chemotherapy was also identified as the most significant predictive factor for the development of HBV reactivation. The optimal cut-off was found to be at serum HBV DNA level of 3×10^5 copies/ml (by real-time PCR assay), which gave a sensitivity of 81% and a specificity of 85% [90]. In addition, it was recently shown that in Asian patients with hepatocellular carcinoma, a high HBV viral load prior to systemic cytotoxic chemotherapy was an adverse factor, not only with severe hepatitis but with also survival [91].

To obtain a better predictor for postchemotherapy HBV reactivation, we recently investigated the effect of prechemotherapy intrahepatic covalently closed circular DNA (cccDNA) on HBV reactivation. This is because HBV cccDNA serves as the template for the production of HBV pregenomic RNA (pgRNA) [92] and a higher number of replication templates should increase the rate of HBV reactivation under immunosuppression. Using receiver-operating characteristics, the overall accuracy of using intrahepatic cccDNA to predict HBV reactivation was 88.9% (95% confidence interval [CI]: 73.2–100.0%); the optimal cut-off value being 2.1 copies per cell with the sensitivity, specificity, positive predictive value, and negative predictive value of 77.8% (95% CI: 40.0–97.2%), 100% (95% CI: 75.3–100%), 100% (95% CI: 59.0–100%), and 86.7% (95% CI: 59.5–98.3%), respectively. Therefore, quantifying intrahepatic cccDNA will help identify patients at a high risk for HBV reactivation after chemotherapy so that they could be treated with preemptive anti-HBV therapy. However, the facilities and technique required for quantifying intrahepatic cccDNA are not widely available and could only be performed in a few research centers. Also, not all patients could withstand percutaneous liver biopsy as they might have clotting derangement, especially those with hematological malignancy [83]. Another viral factor that has been investigated is hepatitis B e antigen (HBeAg) but the results are conflicting [6, 10, 58, 89, 93–95]. This is probably related to the presence of the precore/core promoter HBV mutants (i.e., HBeAg-negative/hepatitis B e antigen-positive chronic hepatitis B infection) [96]. Studies on the clinical significance of HBV genotypes indicate that genotypes may correlate with key clinical events [97, 98]. However, data are scarce on the incidence of HBV reactivation after chemotherapy, in relationship to HBV genotypes.

Apart from viral factors, the rate of HBV reactivation varies with the nature, duration, and degree of immunosuppression related to the cytotoxic or immunosuppressive agents used. Among the chemotherapeutic agents used, corticosteroids and anthracyclines [1–7] are most frequently associated with HBV reactivation. The HBV DNA contains a glucocorticoid-responsive element that facilitates replication [70, 71], while anthracyclines have been shown in vitro to stimulate HBV DNA secretion [99]. Hence, "steroid free" chemotherapy has been proposed to minimize the risk of HBV reactivation. In a prospective study of 50 patients with aggressive non-Hodgkin lymphoma (NHL) (75% diffuse large B-cell NHL in both the steroid-free and the steroid-inclusive arms, the use of steroid-free chemotherapy resulted in a significant decrease in the rate of HBV reactivation (73% vs. 38%, $P = 0.03$).

Table 1 Risk factors associated with HBV reactivation in HBsAg-positive patients treated with cytotoxic or immunosuppressive therapy, identified by multivariate analysis

Author	Underlying diseases	Rate of HBV reactivation (%)	Risk factors
Yeo et al. [18]	HCC	36	Elevated serum ALT level
Lau et al. [20]	Lymphoma	45	Serum HBV DNA$>10^5$ copies/ml
Jang et al. [89]	HCC	22	Positive serum HBeAg
Nagamatsu et al. [58]	HCC	24	Positive serum HBeAg
Zhong et al. [90]	Various malignancies	26	Lymphoma/breast Ca, Anthracycline/steroid Serum HBV DNA$>10^3$ copies/ml
Hui et al. [83]	Lymphoma	41	High intrahepatic cccDNA

However, patients in the steroid-free arm had a significantly lower rate of complete remission and shorter overall survival, presumably due to suboptimal therapy [100]. Although individual agents may be associated with HBV reactivation through specific mechanisms, the degree of immunosuppression as a consequence of combining these agents with others could also contribute to the development of the condition. This is exemplified in patients treated with BMT, where there is a higher incidence of HBV reactivation when compared with the more commonly used, standard dose of chemotherapy [1–5]. Also, patients with gastrointestinal malignancies who undergo cytotoxic chemotherapy, mainly consisting of less-immunosuppressive agents (fluorouracil and folinic acid), have a lower risk of developing viral reactivation [71], and in HBV-infected patients with hepatocellular carcinoma, the incidence of HBV reactivation appears to correlate with the level of immunosuppression of the anticancer therapy administered; viral reactivation was reported in 40, 25, and 2% of patients who underwent systemic chemotherapy, transatrial chemotherapy, and percutaneous ethanol injection or surgical resection, respectively, in descending order of immunosuppressive effects [58, 89, 101].

Preemptive use of nucleoside analogues

As hepatitis due to HBV virological reactivation is associated or preceded by enhanced HBV viral replication during the immunosuppressive phase, the initiation of antiviral treatment such as lamivudine [102–109] and famciclovir [84, 110] only after there are major biochemical abnormalities is not entirely satisfactory. This may not be effective in reducing liver injury by this time, because the immunologic events causing the flare have already been activated and viral elimination is ongoing [1–6]. Thus, a more proactive approach may be necessary. Recently, many clinical researchers have reported the effectiveness of preemptive lamivudine in reducing the incidence of hepatitis due to HBV reactivation in HBsAg-positive patients treated with immunosuppressive or cytotoxic therapy. From 2002 to 2006, in the literature, there were 13 reports on the use of preemptive lamivudine with untreated controls (Table 2). A meta-analysis of these 13 studies with 702 HBsAg-positive patients (237 treated with preemptive lamivudine and 465 untreated controls), showed that the incidence of hepatitis due to HBV reactivation was 3.3% in the treated group and 35.0% in the untreated control group (odds ratio [OR]: 0.083; 95% CI: 0.045–0.155, $P < 0.0001$). Hence, there is a strong suggestion of a beneficial effect on the administration of preemptive lamivudine in reducing the hepatitis due to HBV reactivation in HBsAg-positive patients treated with cytotoxic or immunosuppressive therapy (Fig. 2). However, the design of these studies was mostly retrospective using untreated controls for comparison. It remains unclear on the timing of when to start preemptive lamivudine therapy. One can administer lamivudine before or at the initiation of cytotoxic therapy and cover the entire period of immunosuppression with anti-HBV nucleoside analogues (early preemptive therapy). Alternatively, one can monitor closely for serological evidence of HBV reactivation and use anti-HBV nucleoside analogues only when there is evidence of HBV virological reactivation (deferred

Table 2 Reports of preemptive lamivudine in HbsAg-positive patients to reduce HBV reactivation after cytotoxic chemotherapy, with historical controls

Author	Underlying disease	Type of chemotherapy	Incidence of HBV reactivation Treated* versus untreated controls
Nagamateu et al. [58]	Hepatocellular carcinoma	Transhepatic intra-arterial chemotherapy	0/8 vs. 6/9
Dai et al. [111]	Breast cancer	Systemic	0/11 vs. 5/9
Shibolet et al. [112]	Various malignancies	Systemic	0/13 vs. 2/5
Persico et al. [113]	Lymphoma	Systemic	0/3 vs. 12/21
Lau et al. [85]	Lymphoma	Systemic	1/20 vs. 9/20
Ozguroglu et al. [114]	Lymphoma	Systemic	0/4 vs. 5/8
Leaw et al. [115]	Lymphoma	Systemic	0/11 vs. 17/61
Yeo et al. [116]	Various malignancies	Systemic	3/65 vs. 48/193
Idilman et al. [117]	Hematological malignancies	Systemic	0/8 vs. 5/10
Lee et al. [118]	Lymphoma	Systemic	1/11 vs. 17/20
Yeo et al. [119]	Breast cancer	Systemic	2/31 vs. 19/61
Lim et al. [127]	Various malignancies	Systemic	0/16 vs. 7/19
Jang et al. [88]	Hepatocellular carcinoma	Transhepatic intra-arterial chemotherapy	1/36 vs. 11/37

* Pre-emptive lamivudine therapy

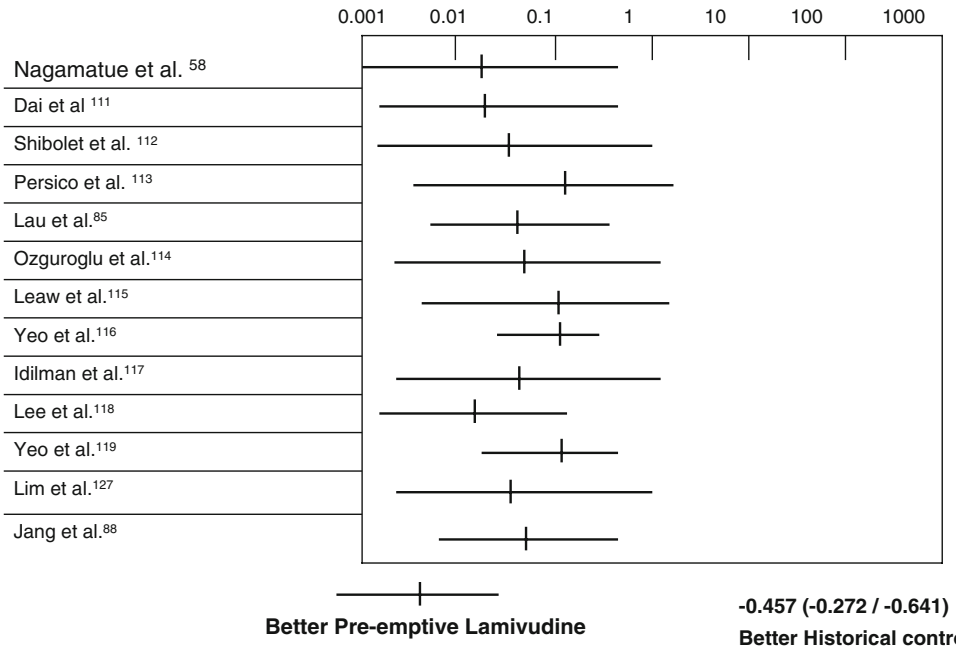

Fig. 2 A meta-analysis of 13 studies reported during 2002–2006 that compare preemptive use of lamivudine versus historical controls in hepatitis B surface antigen-positive patients treated with systemic chemotherapy or transhepatic intraarterial chemotherapy. Altogether, 702 hepatitis B surface antigen-positive patients (237 treated with preemptive lamivudine and 465 untreated controls) were recruited. Those patients treated with preemptive lamivudine had a significantly lower incidence of hepatitis due to HBV reactivation (3.3%) than the untreated controls (35.0%; OR 0.083; 95% CI: 0.045–0.155; $p < 0.0001$). Hence, there is a strong suggestion of a beneficial effect on the administration of preemptive lamivudine in reducing the hepatitis due to HBV reactivation in HBsAg-positive patients treated with cytotoxic or immunosuppressive therapy

preemptive therapy) [56, 86]. Although early preemptive therapy reduces the need to closely monitor the serum HBV DNA level, it runs the risk of overtreating at least half of the patients with nucleoside analogues who would not develop HBV reactivation. In addition, the duration of therapy with nucleoside analogues, such as lamivudine, would be longer with this approach and this could increase the risk of developing HBV viral resistance, as the incidence of viral resistance increases with prolonged antiviral therapy [67]. On the other hand, although the latter approach is more scientific, there are a few shortcomings. First, patients could still have hepatitis due to HBV reactivation with this approach. Second, the need for very close monitoring of serum HBV DNA by expensive or labor-intensive quantitative assay could be a problem when there is a lack of such laboratory support. Third, with the poor understanding of viral and T-cell kinetics in hepatitis due to HBV reactivation, the frequency of monitoring has been poorly defined. To explore the optimal time to initiate lamivudine in these settings, we studied 30 consecutive HBsAg-positive lymphoma patients treated with intensive cytotoxic therapy and randomized (1:1) them to receive either lamivudine 100 mg daily 1 week before chemotherapy or to have this treatment deferred until there was serological evidence of HBV reactivation on the basis of serial 2-week-interval serum hepatitis B virus DNA monitoring by a Digene Hybrid Capture II assay. It was found that early is preferable to deferred preemptive lamivudine therapy for HBsAg-positive patients undergoing chemotherapy, with a significantly lower incidence of HBV virological reactivation after chemotherapy. Almost all patients (87.5%) in the "deferred" treatment group suffered from hepatitis (5 anicteric hepatitis, 1 icteric hepatitis, and 1 hepatic failure), despite being treated with lamivudine at the time of detection of HBV virological reactivation. Currently, this early preemptive approach with the use of lamivudine has been adopted by the major HBV treatment guidelines [120–122].

It remains speculative whether monitoring the serum HBV DNA at a closer interval, with a more sensitive HBV DNA assay, would improve the situation [123]. The major concerns related to the use of this early preemptive approach have been the prolonged use of lamivudine and the unnecessary treatment for some patients who may not develop HBV reactivation. This will lead to the development of lamivudine resistance caused by point mutations, with substitution of either valine or isoleucine for the amino acid position 204 methionine (rtM204V or rtM204I, respectively) in the HBV DNA polymerase gene (tyrosine–methionine–aspartate–aspartate [YMDD] motif) [67]. Its risk increases as the therapy is prolonged, reaching a level of 67% after 4 years in nonimmunocompromised patients

[67]. In particular, the fact that YMDD mutant infection is occasionally associated with rapid clinical deterioration after transplantation raised additional concern [124, 125]. To avoid this problem, one may use alternative nucleos(t)ides analogues that are associated with less viral resistance, such as adefovir, entecavir, and telbuvidine [67].

How long should we keep the patients on lamivudine?

As the mechanism of nucleos(t)ide analogues in inhibiting viral replication is direct suppression of HBV polymerase activity and has little effect on the restoration on host immune control [67], its premature withdrawal could lead to rapid rebound of viral replication, resulting in liver-related morbidity and mortality [126]. On the other hand, prolonged therapy with nucleos(t)ide analogues is associated with an increased likelihood of developing lamivudine-resistant mutants. Hence, most cancer centers would aim at discontinuing or withdrawing preemptive lamivudine as soon as possible to limit the duration of antiviral therapy [57, 85, 86, 111–119, 127]. However, at the moment there is no available consensus on the optimal duration of lamivudine therapy. This is mostly due to the lack of data on occurrence of hepatic flares after the withdrawal of preemptive antiviral therapy in these patients. As HBV reactivation after cytotoxic or immunosuppressive therapy is usually accompanied by an upsurge of white cell counts from the nadir, our center has adopted a protocol of only withdrawing lamivudine once the total white cell count has normalized and at least 3 months after completion of chemotherapy [56]. The concept of this protocol or approach is to cover the entire period when the host interaction with HBV has been disturbed as a result of the cytotoxic or immunosuppressive therapy. This way, we would only be withdrawing lamivudine after the host's immune system has recovered sufficiently to the prechemotherapy state. Recently, we examined the occurrence of hepatic flares after withdrawal of preemptive lamivudine and determined what factors are associated with hepatic flares after withdrawal of preemptive lamivudine. We studied forty-six consecutive HBsAg-positive patients treated with preemptive lamivudine, started one week before initiation of chemotherapy and continued for the entire duration of chemotherapy. Preemptive lamivudine was stopped at a median 3.1 (range 3.0–3.4) months after completion of chemotherapy. Patients were longitudinally followed up after withdrawal of preemptive lamivudine. Median time of follow-up after withdrawal of lamivudine was 25.7 (range 5.7–75.7) months. Eleven of the 46 patients (23.9%) developed HBV reactivation after withdrawal of preemptive lamivudine. Eight of 16 patients with high prechemotherapy HBV DNA ($>10^4$ copies/ml) compared with 3 of the 30 patients with low prechemotherapy HBV DNA ($\leq 10^4$ copies/ml) developed HBV reactivation (50.0% vs. 10.0%, respectively; $P = 0.001$). Hepatitis B e antigen-positive patients were also more likely to develop HBV reactivation (5/11 [45.5%] vs. 6/35 [17.1%], respectively; $P = 0.041$). A high prechemotherapy HBV DNA ($>10^4$ copies/ml) was the most important risk factor for HBV reactivation after withdrawal of preemptive lamivudine on Cox proportional hazards analysis (relative risk 16.13; 95% CI 2.99–87.01; $P = 0.001$). Hence, HBV reactivation is more likely to occur in patients with high prechemotherapy HBV DNA after withdrawal of preemptive lamivudine [87]. On the basis of these results, in our center we will keep those patients with high pretreatment HBV DNA level ($>10^4$ copies/ml) on nucleos(t)ide analogues for a longer period of time until there is evidence of restoration of host immune control on the virus, such as e-seroconversion or even s-seroconversion (Fig. 3).

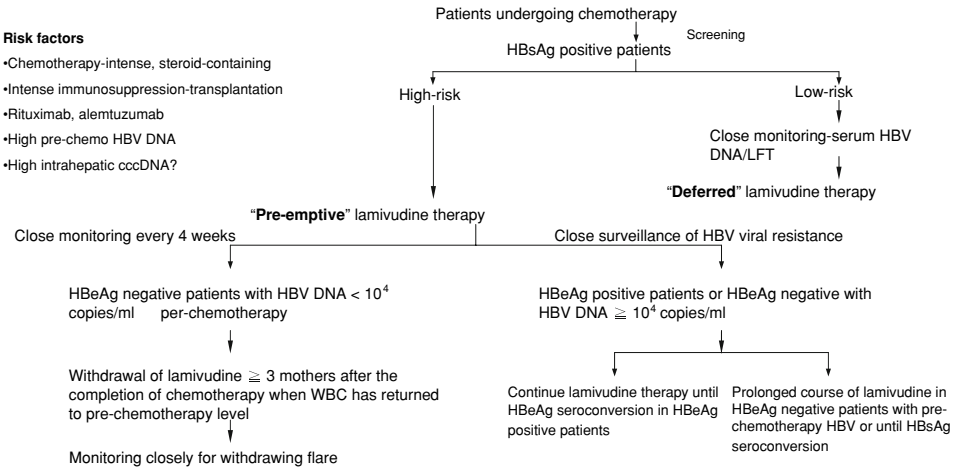

Fig. 3 Algorithm for management of hepatitis B surface antigen-positive patients treated with a cytotoxic or immunosuppressive agent. HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen

Future direction

In the future, education of the medical profession to screen for HBsAg-positive status before initiation of cytotoxic chemotherapy or immunosuppressive therapy should be enhanced. On the research side, identification of viral or host determinants of HBV reactivation would further facilitate and improve the management of this important clinical problem, especially in the Asia-Pacific region. In addition, the application of other nucleos(t)ide analogues with more potent antiviral effect and less resistance will need to be explored.

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