Hepatitis B reactivation in the setting of chemotherapy and immunosuppression - prevention is better than cure

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Abstract

Due to the inherent relationship between the immune system and the hepatitis B virus (HBV) in exposed and infected individuals, immunomodulation associated with the treatment of solid tumours, haematological malignancies and inflammatory disorders has been linked to HBV reactivation (HBVr). Reactivation of HBV infection in the setting of chemotherapy and immunosuppression may lead to fulminant liver failure and death, but there is a cumulative body of evidence that these are potentially preventable adverse outcomes. As chronic hepatitis B is largely asymptomatic but also endemic worldwide, clinicians caring for patients requiring chemotherapy or immunosuppression need to be vigilant of the potential for HBVr in susceptible individuals. Serological screening and prophylactic and pre-emptive antiviral treatment with a nucleos(t)ide analogue should be considered in appropriate settings. Hepatitis B prevalence is examined in this review article, as are the risks of HBVr in patients receiving chemo- and immunosuppressive therapy. Recommendations regarding screening, monitoring and the role of antiviral prophylaxis are outlined with reference to current international associations' guidelines and the best available evidence to date.

Key words: Immunosuppression; Hepatitis B; Hepatitis B virus reactivation; Prophylaxis; Lamivudine; Chemotherapy; Entecavir; Tenofovir; Rituximab

Core tip: Hepatitis B virus reactivation is a potentially fatal but preventable complication of chemotherapy and immunosuppression. Both chronically infected [hepatitis B surface antigen (HBsAg) positive] and previously exposed (HBsAg negative/anti-HBc positive) patients are susceptible, the risk observed to be strongly associated with the potency of the immunosuppressive drug regime and the baseline virological status. The knowledge gaps that require further investigation in the optimal management of this phenomenon are discussed in this review. Recommendations regarding screening, monitoring and the role of antiviral prophylaxis are outlined with reference to current international associations’ guidelines and the best available evidence to date.
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HEPATITIS B EPIDEMIOLOGY

It is estimated that 2 billion people have been infected with hepatitis B worldwide; of these, 350 million of these are chronically infected [chronic hepatitis B (CHB)]\(^1\). Seventy-five percent of the chronically infected reside in the Asia-Pacific region, where the disease is endemic\(^2,3\). Across the globe, northern, western, and central Europe, North America and Australia have the lowest prevalence of chronic hepatitis B virus (HBV) infection [hepatitis B surface antigen (HBsAg) positive 0.2%-0.5%] and HBV exposure (HBsAg negative but anti-HBc positive 4%-6%); Eastern Europe, the Mediterranean, Russia, Southwest Asia, Central and South America have higher rates (2%-7% chronically infected and 20%-55% exposed) and the highest rates are documented in China, Southeast Asia and tropical Africa (8%-20% chronically infected and 70%-95% exposed)\(^4\). The Centre for Disease Control (CDC) advises the high-risk groups in the general population (Table 1) who should be screened and managed for chronic HBV infection\(^5\).

HBV INFECTION AND THE IMMUNE SYSTEM

\textbf{HBsAg positive patients}

Chronic HBV infection is characterised by the interaction between the virus, the immune system and the liver itself. This interaction is one that may change spontaneously over time, resulting in the 4 phases of CHB infection [the Hepatitis B e-antigen (HBeAg) positive phases of immune tolerance and immune clearance; the HBeAg negative phases of immune control and immune escape] and the corresponding hepatic consequences\(^5\). This interaction between virus and host may also be disrupted by any drug-induced modulation of the immune system resulting in HBV reactivation (HBVr), which has the potential to cause significant liver injury.

The liver injury that occurs as a result of a HBVr may arise from two mechanisms\(^6\). Loss of immune control of the virus during chemo- or immunosuppressive therapy may result in uncontrolled viral replication, with rapid rises in HBV-associated proteins causing overwhelming direct cytolytic destruction of hepatocytes. Alternatively, after cessation of chemotherapy, reconstitution of the immune system may cause severe immune-mediated injury to infected hepatocytes. The exaggerated immune response against hepatocytes expressing hepatitis B viral proteins may cause overwhelming necrosis of liver cells. The reactivation may be delayed, occurring as late as six months after the cessation of chemotherapy. In the case of certain treatment regimens (e.g., rituximab due to prolonged immunosuppression and immune reconstitution phases) reactivation can occur as late as 12 mo post-treatment\(^7,8\). HBVr presents clinically as a spectrum of asymptomatic biochemical hepatitis through to the more concerning acute symptomatic hepatitis with the potential for liver failure and death\(^9\).

\textbf{HBsAg negative, anti-HBc positive patients}

Individuals known to have CHB (HBsAg positive) may spontaneously lose HBsAg at an annual rate of 0.5%; this is defined as "spontaneous clearance"\(^10\). Alternatively, patients may have serological evidence of past HBV exposure, both scenarios leading to an HBsAg negative/anti-HBc positive state. These patients by far outnumber those with CHB across the globe\(^1\). The HBV may persist in hepatocytes and other tissues in the form of covalently closed circular DNA. Although the HBV DNA may not be detectable in serum, they remain at risk of HBVr in the setting of chemo- or immunosuppressive therapy, and the clinical adverse outcomes as described above\(^11,12\).

\textbf{The significance of anti-HBs}

Anti-HBs antibodies may develop in HBsAg negative/anti-HBc positive individuals indicating the development of natural immunity or in anti-HBc negative individuals who have been immunised against HBV. There is limited evidence to date that the presence of anti-HBs protects against HBVr. In one small study of 29 lymphoma patients, no patient (0/10) with an anti-HBs titre of >100 IU/mL experienced HBVr, and lower anti-HBs titre was independently associated with HBVr\(^13\). In patients receiving haematopoetic stem cell transplantation, the donor anti-HBs titre was associated with a decreased risk of HBVr\(^14\). These findings are yet to be validated. Until then, management decisions on the prophylaxis of HBVr cannot be made on the basis of the presence or titre of anti-HBs.

DEFINITIONS OF HBVr AND ASSOCIATED CLINICAL ENDPOINTS

HBVr has been variably defined across the existing studies examining this phenomenon. The HBV DNA assays used have varied in their lower limits of detection, potentially underestimating the prevalence of HBVr and delaying the time point at which HBVr may be first detected thereby limiting the ability to directly compare the results across studies. “Hepatitis” has been variably reported as alanine aminotransferase (ALT) elevation above upper limit of normal, or by “fold” increases from baseline; whether the hepatitis is symptomatic or asymptomatic is inconsistently documented. Suggested definitions for HBVr are listed beneath, however a consensus is yet to be reached for
HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HIV: Human immunodeficiency virus.

Table 1  Populations at high risk for hepatitis B virus infection that should be screened14,15

| Individuals born in areas of high (≥ 8%) or intermediate prevalence (2%–7%) for HBV (HBsAg positive) including immigrants and adopted children |
| Asia, Africa, South Pacific Islands: All countries |
| Middle East (except Cyprus and Israel) |
| Eastern Europe: All countries except Hungary |
| European Mediterranean: Malta and Spain |
| The Arctic (indigenous populations of Alaska, Canada, and Greenland) |
| South America: Ecuador, Guyana, Suriname, Venezuela, and Amazon regions of Bolivia, Brazil, Colombia, and Peru |
| Caribbean: Antigua and Barbuda, Dominica, Granada, Haiti, Jamaica, St. Kitts and Nevis, St. Lucia, and Turks and Caicos |
| Central America: Guatemala and Honduras |
| Other groups recommended for screening |
| United States born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (8%) |
| Household and sexual contacts of HBsAg-positive persons |
| Persons who have ever injected drugs |
| Persons with multiple sexual partners or history of sexually transmitted disease |
| Men who have sex with men |
| Inmates of correctional facilities |
| Individuals with chronically elevated ALT or AST |
| Individuals infected with HCV or HIV |
| Patients undergoing renal dialysis |
| All pregnant women |
| Persons needing immunosuppressive therapy |

HBV reactivation with chemotherapy

Another important clinical outcome (and relevant endpoint for future studies) is the interruption of chemo- or immunosuppressive therapy, which may be indicated upon the occurrence of HBVr. In a study of 41 patients with breast cancer, HBVr was diagnosed in 17 (41%), and treatment interruption occurred in 71% of these cases (compared with only 33% of those that did not experience HBVr; \( P = 0.019 \)).18 Treatment interruption has the potential to increase morbidity and mortality associated with the underlying malignancy or disease process. Due to a lack of reporting of the occurrence of treatment interruption and the long-term outcomes of cancer- or disease-related morbidity and mortality in the majority of studies of HBVr, the impact of treatment interruption due to HBVr across diseases is not clear and requires further evaluation.

THE MAGNITUDE OF THE RISK OF HBVr

Clinically significant reactivations of HBV have been documented in both cancer and non-cancer patients receiving chemo- or immunomodulating pharmacotherapy. The majority of the studies reporting the rates of HBVr are case reports or small case series using variable definitions of HBVr, hence leading to a broad range of prevalences cited.

Reactivation of HBV has been reported in patients treated for lymphoma, other haematological malignancies and in the setting of haematopoetic stem cell transplant4,14,19-22. The prevalence of CHB in patients with lymphoma has been reported as high as 26%15. HBVr can occur in 38%-73% of HBsAg positive patients being treated for lymphoma, the higher HBVr rates seen in patients being treated with chemotherapy regimes including high dose corticosteroids23-26. Patients who receive a bone marrow transplant (BMT) or haematopoetic stem cell transplant (HSCT) for haematological malignancy are a special population that experience prolonged immunosuppression related to the conditioning chemotherapy leading up to the transplant, post-transplant immunosuppressive therapy as well as a potentially protracted immunodeficient state while engraftment occurs. Fatal HBVr has been observed in HBsAg positive patients, as well as HBsAg negative/anti-HBc positive patients25,26. In a multicentre retrospective study of patients receiving both autologous and allogeneic stem cell transplantation, the rates of HBVr at 2 years post-transplant were 66% and 81% respectively; the majority of the reactivations occurred within the first 12 mo post-transplant27.

Therapy for solid tumours including breast, nasopharyngeal and hepatocellular cancer (the latter in the setting of either systemic chemotherapy or trans-arterial chemoembolisation) has also been associated with HBVr.28-30. Amongst a cohort of oncology patients with solid tumours, CHB was documented in 12% of patients15. These investigators observed that approximately 20% of death.
CHB patients receiving chemotherapy for their malignancy experienced HBVr. Forty-one percent of breast cancer patients positive for HBsAg have been reported to experience HBVr.[48]

HBVr has been reported in patients receiving immunosuppression for inflammatory bowel disease,[37,38] rheumatological diseases (rheumatoid arthritis, ankylosing spondylitis)[39–44], dermatological disorders (psoriasis)[45], autoimmune disorders[46,47] and in those following solid organ transplantation (e.g., renal and liver).[48–52]

FACTORS ASSOCIATED WITH HBVr

Elucidating the risk factors for HBVr amongst those receiving chemotherapeutic or immunosuppressive therapy may help to identify cases that should receive antiviral prophylaxis. Patient-specific risk factors associated with reactivation include younger age, male gender and the type of treatment regimen prescribed.[9,53,54]. Virological and serological status

Detectable HBV DNA, HBsAg, HBeAg and anti-HBc are important virological and serological markers strongly associated with HBVr.[10–12,17,55]. High HBV DNA is the strongest of these risk factors, and HBsAg positive patients are up to 8 times more likely to experience HBVr than HBsAg negative/anti-HBc positive patients.[20,56,57]. Amongst HBsAg positive patients, HBeAg positive patients have been observed to be more likely to experience HBVr than HBeAg negative patients.[56]. The HBV genotype appears to be significant in that HBV genotypes C and B (prevalent in East Asia but rare in Caucasians) correlate with HBVr.[10,58,59]. The latter observations may simply be a reflection of the prevalent genotypes in these geographical regions and requires further investigation.

Mutations of the HBsAg may confer risk of HBVr.[60]. In a recent study of 93 patients with CHB (29 of whom developed HBVr) the HBsAg genetic features were analysed. HBsAg-mutations localised in immuno-active HBsAg regions were observed in 76% patients who experienced HBVr (vs 3.1% controls, P < 0.001). Of the 13 HBsAg-mutations found in these patients, 8 are known to block HBsAg-recognition by the humoral immune pathway and the remaining 5 mutations were identified within in Class- I / II-restricted T-cell epitopes (potentially influencing T-cell mediated responses to HBV-escape).[60]. These observations suggest that patients infected with HBV expressing such HBsAg-mutations may be more able to overcome the normal immune response, thereby being more at risk of HBVr with chemotherapy. The clinical application of these findings is yet to be determined.

Chemotherapy/Immunosuppression drug class

The pharmacotherapy used to manage malignant and inflammatory conditions is rapidly evolving with new and targeted agents being developed. Several of these newer agents have the potential to disrupt the control that the immune system has over any underlying HBV exposure or chronic infection. Clinical evidence of HBVr with these agents has subsequently been apparent in case reports and case series. A list of the drug classes listed from most potent to least potent of the agents is yet to be determined.

Table 2 Immunosuppressive drug classes and corresponding risk estimates of hepatitis B virus reactivation[63,80]

| Drug class                      | Drug                        | Risk estimate of HBVr for HBsAg positive | Risk estimate of HBVr for HBsAg negative/anti-HBc positive |
|---------------------------------|-----------------------------|-----------------------------------------|------------------------------------------------------------|
| B-cell depleting agents         | Rituximab (anti-CD20)       | High (30–60%)                           | High (> 10%)                                               |
|                                 | Ofatumumab (anti-CD20)      | Moderate (1%)                           | Moderate (1%)                                              |
| Anthracycline derivatives       | Doxorubicin                 | Moderate (1–10%)                         | Moderate (1%)                                              |
|                                 | Epirubicin                  | Moderate (1%)                           | Moderate (1%)                                              |
| TNF-α inhibitors                | Infliximab                  | Moderate (1%)                           | Moderate (1%)                                              |
|                                 | Etanercept                  | Moderate (1%)                           | Moderate (1%)                                              |
| Cytokine inhibitors and integrin inhibitors | Abatacept (anti-CD80, -46) | Moderate (1%)                           | Moderate (1%)                                              |
|                                 | Ustekinumab (anti-IL-12, -23)| Moderate (1%)                           | Moderate (1%)                                              |
|                                 | Natalizumab (binds α4-integrin) | Moderate (1%)                           | Moderate (1%)                                              |
|                                 | Vedolizumab [binds integrin α4][67 (LPAM-1)] | Moderate (1%)                           | Moderate (1%)                                              |
| Tyrosine kinase inhibitors       | Imatinib                    | Moderate (1%)                           | Moderate (1%)                                              |
|                                 | Nilotinib                   | Moderate (1%)                           | Moderate (1%)                                              |
| Corticosteroids                 | High dose, e.g., prednisone ≥ 20 mg for ≥ 4 wk | High (> 10%)                           | NA                                                         |
|                                 | Moderate dose, e.g., prednisone < 20 mg for ≥ 4 wk | Moderate (1%)                           | Moderate (1%)                                              |
|                                 | Low dose, e.g., prednisone for < 1 wk | Low (< 1%)                             | Low (< 1%)                                                |
|                                 | Intra-articular corticosteroids | Low (< 1%)                             | Low (< 1%)                                                |
| Traditional immunosuppression   | Azathioprine                | Low (1%)                                | Low (< 1%)                                                |
|                                 | 6-mercaptopurine            | Low (1%)                                | Low (< 1%)                                                |
|                                 | Methotrexate                | Low (1%)                                | Low (< 1%)                                                |

TNF: Tumour necrosis factor; IL: Interleukin; LPAM: Lymphocyte Peyer’s patch adhesion molecule; NA: Not available; HBVr: Hepatitis B reactivation; HBsAg: Hepatitis B surface antigen.
used to treat haematological malignancy, however rituximab has been used for non-malignant autoimmune and neurological diseases. Both HBsAg positive and HBsAg negative/anti-HBc positive patients who receive these agents appear to be susceptible to HBVr. The rate of HBVr with these agents in HBsAg negative/anti-HBc positive patients has been reported at 16.9%, and seroreversion rate of 20%-40%. HBVr has occurred up to 12 mo after cessation of B-cell depleting drugs (and in a small number of cases delayed beyond 12 mo) indicating the potency of the immunosuppressive effect of this drug class and the prolonged immune reconstitution phase. A study of 63 HBsAg negative/anti-HBc positive patients with haematological malignancy who received rituximab without antiviral prophylaxis has been reported. At 2 years, 41.5% had experienced HBVr which occurred at a median of 23 (range 4-100) wk after rituximab treatment. These observations would indicate that any monitoring or antiviral prophylaxis prescribed to these patients may require longer duration than other classes of immunosuppressive drugs.

Tumor necrosis factor (TNF)-alpha inhibitor agents include infliximab, etanercept and adalimumab, which have been used in the management of inflammatory bowel disease, rheumatological disease and psoriasis (amongst other disorders). All 3 drugs have been associated with HBVr. The absolute risk of HBVr with these agents is not clear owing to the heterogeneity of the cases and cohorts reported. A larger study of 257 cases exposed to anti-TNF agents for a variety of indications reported a HBVr rate of 39% in HBsAg positive patients and 7 fold lower rate of HBVr in anti-HBc positive patients. Cytokine and integrin inhibitors, by virtue of their interaction with the immune system, have also been associated with HBVr. Drugs of this class and their target molecules are listed in Table 2. Evidence of role of these drugs in HBVr exists largely as case reports and small case series.

Tyrosine kinase inhibitors including imatinib and nilotinib are used to treat chronic myeloid leukaemia and gastrointestinal stromal tumours. Evidence of HBVr is limited, again, to case reports and small case series.

Corticosteroids are the most longstanding and hence most commonly used of the immunosuppressants across all the aforementioned disease processes. In addition to their effect on T-cell function, corticosteroids directly enhance HBV replication through their interaction with the HBV glucocorticoid responsive element (a transcriptional regulatory element). Although steroids are administered at a range of dosages and durations for a variety of indications, it has been observed that a 4-wk course of prednisone has been associated with HBVr in the post-withdrawal (immune reconstitution) phase and worsened liver histology. Chronic steroid use in the setting of chronic airways disease is associated with HBVr in 11.1% of those treated with oral steroids and 3.2% of those treated with inhaled steroids.

In the aforementioned study (including 198 patients with asthma or chronic obstructive pulmonary disease) continuous oral corticosteroid therapy (> 3 mo) and high-dose (defined as > 20 mg prednisone/day) were associated with HBVr with OR of 5.7 and 4.9 respectively, when compared with HBVr in those receiving inhaled corticosteroids. Low dose, short term (< 2 wk) administration of oral (systemic) corticosteroids, intraarticular injection and topical therapies have not been associated with HBVr. These data taken together indicate that corticosteroids have the potential to induce HBVr but that the risk varies according to the dose, duration and route of administration of the drug.

"Traditional" immunomodulating drugs such as azathioprine, 6-mercaptopurine and methotrexate appear to have the lowest potential for HBVr. There are no documented cases of HBVr with the use of azathioprine or 6-mercaptopurine monotherapy. Cases of HBVr have been reported with methotrexate, however corticosteroids or other immunomodulators were co-administered in most instances, compounding the risk of HBVr.

The risk of HBVr associated with each of the drug classes administered to HBsAg positive or HBsAg negative/anti-HBc positive patients has been estimated by the American Gastroenterological Association (AGA) based on a thorough systematic review of the existing literature. This risk stratification is summarised in Table 2. The risk of HBVr may be stratified to high (> 10% risk of HBVr), moderate (1%-10%) and low (< 1%). The current AGA recommendations are based on the risk of HBVr according to the combination of serological markers of HBV and the chemotherapy/immunosuppression regimen prescribed and, to date, are the most detailed and specific recommendations with regard to the patient risk groups in whom antiviral prophylaxis should be considered.

**Hepatitis B and delta co-infection**

To date, only a single case report of hepatitis delta (HDV) reactivation in association with HBVr exists. This patient was co-infected with hepatitis C (HCV RNA positive), HBV (HBsAg positive, HBV DNA undetectable at baseline) and had evidence of cleared HDV infection (anti-HDV positive). A rituximab-CHEOP regime was prescribed to treat lymphoma; HBV DNA became detectable during chemotherapy. Subsequently, 15 mo after chemotherapy, HDV RNA was detected at a level of 77.6 million copies/mL. The patient was managed successfully with lamivudine, which was in turn switched to emtricitabine/tenofovir. Given the singularity of this report, there is no real evidence base to guide the management of HBV-HDV co-infection in this setting and patients should be managed according to their HBV status.

**MANAGEMENT OF HBVr**

HBVr occurring during chemo- or immunosuppressive therapy, if detected, may be an indication to delay
or cease therapy. Withholding chemotherapy may halt or reduce the rate of HBV replication potentially abrogating the HBVr. As discussed, in the absence of antiviral prophylaxis, HBVr may also occur in the post-chemotherapy immune reconstitution phase.

The role of antiviral therapy once HBVr is already established has been investigated by several groups. In a prospective study of patients treated for non-Hodgkin’s lymphoma, lamivudine therapy started when ALT elevation was detected did not change the natural course of HBVr; 2 patients in this cohort died despite lamivudine use at the onset of HBVr[63]. Numerous case reports and series describe death due to liver failure despite the introduction of lamivudine at the onset of HBVr[62–66]. Only a few cases of successful treatment of HBVr with entecavir have been published[87–89]. Despite the paucity of data regarding the efficacy of entecavir to treat established HBVr (and no data to date regarding tenofovir), the ability of these drugs to rapidly reduce HBV DNA make them attractive alternatives to lamivudine in patients who experience HBVr to potentially abrogate the risk of liver failure and mortality. Data on the efficacy and cost-effectiveness of these approaches to management are needed.

PREVENTION OF HBVr

Given the poor outcomes associated with reactionary treatment of HBVr (i.e., antiviral treatment once HBVr is already established), strong consideration must be given to the role of antiviral prophylaxis in at-risk patients who will receive chemo- or immunosuppressive therapy.

A systematic review of studies examining the role of antiviral prophylaxis in chemotherapy patients concluded that lamivudine prophylaxis (vs no prophylaxis) is associated with a relative risk of 0.0–0.21 for HBVr and 0.0–0.2 for death attributable to HBV[90]. Liver failure was not observed in any patient who received lamivudine prophylaxis[90]. In line with these observations, a subsequent systematic review reported that patients given lamivudine prophylaxis during chemotherapy showed an 87% decrease in HBVr compared to patients not given prophylaxis[91]. It is noteworthy to mention that the number needed to treat to prevent one reactivation was just 3 patients[91]. Treatment delay and early cessation of chemotherapy due to HBVr were also reduced by 92% in those who received lamivudine[91].

Most recently, a systematic review and meta-analysis of 5 randomised controlled trials comparing antiviral prophylaxis to treatment at the onset of HBVr has been published[63]. Lamivudine was used in 4 studies and entecavir was used in 1 study[89,92–95]. The overall risk ratio (RR) favoured the prophylactic use of antivirals over no antivirals [RR = 0.13 (0.06–0.30)]63. Antiviral prophylaxis was also associated with a significant risk reduction of hepatitis flare [RR = 0.16 (0.06–0.42)]63.

Owing to the fewer occurrences and lower severity of HBVrs, the use of lamivudine prophylaxis has been deemed to be a cost-effective intervention. The cancer death rate in patients who receive prophylaxis is also reduced, presumably due to the reduced rate of chemotherapy interruption or curtailment[96]. The cost-effectiveness of entecavir and tenofovir have not, as yet, been evaluated.

The duration of antiviral prophylaxis remains under debate. As discussed, delayed HBVr has been observed in patients 6–12 mo after completion of chemotherapy (in the absence of antiviral prophylaxis) in both HBsAg positive and HBsAg negative/anti-HBc positive patients, and also when the antiviral prophylaxis has been curtailed to 2 mo post-completion of antiviral therapy[81]. The duration of risk of HBVr appears to be strongly related to the potency of treatment regime, again mentioning that patients who have received B-cell depleting agents appear to be susceptible to delayed HBVr (up to 12 mo post-treatment and beyond)[20]. Hence, antiviral prophylaxis may be required for at least 6 mo after cessation of chemo- or immunosuppressive therapy and for at least 12 mo for those receiving B-cell depleting agents; subsequent monitoring for delayed HBVr after cessation of antiviral prophylaxis is essential.

Mention must be made of the role of antiviral prophylaxis in recipients of bone marrow or haematopoetic stem cell transplants. Both lamivudine and entecavir have been used with the aim of preventing HBVr in these cases[97–101]. The optimal timing of withdrawal of antiviral prophylaxis, however, remains unclear. HBVr has been observed as early as 12 wk post-discontinuation of lamivudine in the bone marrow transplant setting[98]. In a study of 16 patients who received lamivudine for a median of 73 wk (range 19–153) after stem cell transplantation, the cumulative rate of HBVr at 30 mo follow-up was 20%; 63% of the patients developed documented lamivudine resistance and one patient had virological breakthrough during the study period[99]. HBVr has been diagnosed as late as 4 years after transplantation in a patient who was anti-HBs positive at baseline[102]. It would appear that BMT/HSCT recipients are potentially at risk of HBVr for years after the transplant and consideration must be given to whether these patients require antiviral therapy long term. If therapy were to continue long term, then consideration must be given to the risk of lamivudine resistance, and hence entecavir and tenofovir may be more suitable choices for antiviral prophylaxis due to their high barrier for drug resistance. The current evidence base to address these issues is weak, and further study is required. Of the major international associations’ guidelines, only the European Association for the Study of Liver Disease (EASL) guidelines (2009) provide a recommendation for this patient population: that nucleos(t)ide analogue prophylaxis is recommended for anti-HBc positive patients receiving bone marrow or stem cell transplantation (grade of recommendation C2); a duration of therapy is not specified[103].

Based on the available data, prophylactic antiviral
therapy in the appropriate candidates appears to reduce the risk of HBVr and morbidity. Further studies are required to determine the impact on overall and cancer-related survival and the cost effectiveness of the strategies employed (drug choice, duration of therapy).

**CHOICE OF ANTIVIRAL AGENT**

The drugs currently available for the management of chronic hepatitis B include lamivudine, adefovir dipivoxil, entecavir, telbivudine and tenofovir disoproxil fumarate. By far, the largest body of literature on the prevention of HBVr examines the role of lamivudine, the first of these drugs to be available. The downside of lamivudine use is the high rate of drug resistance (and potential for virological breakthrough or relapse) reported to be 20% within the first 12 mo of use. Fatal HBVr despite lamivudine prophylaxis owing to the development of the M204 drug resistance mutation has been reported in a patient who received R-CHOP for lymphoma[104]. Lamivudine may have a role where total chemotherapy and post-chemotherapy follow-up duration spans less than 12 mo (thereby reducing risk of drug resistance and virological breakthrough), the HBV DNA is undetectable at baseline and the patient is not receiving any of the “high risk” treatment regimes. The latter approach requires further evaluation, but may be an attractive strategy, e.g., in countries with high prevalences of HBV where the cost of the more potent antivirals may be prohibitive.

With substantially lower antiviral resistance rates than lamivudine, entecavir and tenofovir may be a more suitable first line for HBV DNA suppression in those with high pre-chemotherapy HBV DNA levels in order to mitigate HBVr. There are five studies to date comparing entecavir to lamivudine or no prophylaxis in patients with haematological malignancy or lymphoma alone[92,105-108]. Lower rates of HBVr are generally observed with the use of entecavir in these studies, however these studies vary in their design (ranging from retrospective audit to randomised-controlled study) and hence the strength of their findings. In the single randomised controlled study (published in abstract form), 61 patients who received entecavir prophylaxis were compared to 60 patients who received lamivudine[92]. Entecavir was associated with a relative risk reduction of 0.22 (0.08-0.61) for HBVr and had significantly fewer chemotherapy interruptions (1.6% vs 18.3%)[92]. Further data is awaited, as are studies on the role of tenofovir in this setting, but it is expected that given the limitations of lamivudine, entecavir and tenofovir will have a greater role in the prevention of HBVr in the future.

The data regarding adefovir and telbivudine in the prevention and management of HBVr is limited to the liver transplantation setting and is outside of the scope of discussion of this review. These drugs are not recommended as first line drugs for prophylaxis of HBVr in the context of chemotherapy or immunosuppression.

**SCREENING FOR HBV PRIOR TO CHEMOTHERAPY OR IMMUNOSUPPRESSION**

Given the risk of HBVr in patients previously exposed or chronically infected with HBV and receiving chemotherapy or immunosuppression, it is essential for clinicians caring for such patients to be aware of this risk and screen for HBV in order to institute appropriate prophylactic therapy or monitoring. Additionally, screening may uncover previously unrecognized chronic hepatitis B infection and subsequently the complications of cirrhosis and hepatocellular cancer. These liver-related complications require long-term and directed management and may influence the management underlying malignancy/disease.

There are several approaches to screening for HBV in this patient population: (1) Screen all patients prior to chemotherapy/immunosuppression[103,109]. This strategy would identify patients who would potentially benefit from: Antiviral prophylaxis; HBV serology and HBV DNA monitoring (without antiviral prophylaxis); Immunisation against HBV; Evaluation for complications of CHB; Contact tracing of family members for CHB and their subsequent management; (2) Screen only patients at risk of HBV according to CDC “high risk” groups (Table 1)[92,107]; and (3) Screen only patients who, if serological testing was positive, would be prescribed antiviral prophylaxis[63,80,111].

Consideration must also be given to the serological test(s) to be used for screening. The approaches to serological screening for HBV include: (1) Test HBsAg, anti-HBc and anti-HBs. Test HBV DNA if HBsAg or anti-HBc are positive (the latter in case of occult HBV infection); (2) Test HBsAg, anti-HBc only. The role of anti-HBs in HBVr is unclear. Furthermore, immunisation against HBV may not be efficacious during immunosuppression. Therefore, one may argue that anti-HBs status may not be relevant prior to chemotherapy; and (3) Test anti-HBc only. If positive, proceed to test for HBsAg and HBV DNA.

There is a paucity of data on the best and most cost-effective approach to screening for HBV in patients at risk of HBVr. Each of the major international associations has made screening recommendations (summarised in Table 3), which vary across the associations. The most recent and complete of the systematic reviews performed (as at 2014) has estimated risk of HBVr according to specific chemotherapy/immunosuppressive regime, and hence recommends HBV serological screening in patients with moderate to high risk[92,108]. The clinical decision on who and how to screen will likely be influenced by the characteristics of the population being managed and the resources available to the individual, the institution...
Table 3  Comparison of International Associations’ guidelines on the management of hepatitis B virus in the setting of chemotherapy and immunosuppression

| Association guidelines | HBV screening population | Screening test | Antiviral prophylaxis | Antiviral drug recommended | Monitoring in untreated anti-HBc + ve patients |
|------------------------|--------------------------|----------------|-----------------------|---------------------------|-----------------------------------------------|
| American Gastroenterological Association 2014[^80] | High risk of HBVr (>10%) | HBsAg and anti-HBc; HBV DNA if serology + ve | Yes (B1) | Yes (B1) if taking | Drug with high barrier to resistance is favored over lamivudine (B2) |
|                        | B-cell depleting agents |                |                       |                           | No recommendation (knowledge gap) |
|                        | Anthracycline derivatives |                | Continue until at least 6 mo after completion of chemotherapy | B-cell depleting agents | |
|                        | High dose corticosteroids (≥ 20 mg prednisone for ≥ 4 wk) |                |                       |                           | |
| Moderate risk of HBVr (1%-10%) | HBsAg and anti-HBc; HBV DNA if serology + ve | Yes (B2) | Yes (B2) if taking | Drug with high barrier to resistance is favored over lamivudine (B2) | No recommendation (knowledge gap) |
| TNF-α inhibitors |                | Continue until at least 6 mo after completion of chemotherapy | TNF-α inhibitors | |
| Cytokine or integrin inhibitors |                |                       |                       |                           | |
| Tyrosine kinase inhibitors |                |                       |                       |                           | |
| High dose corticosteroids (≥ 20 mg prednisone for ≥ 4 wk) |                |                       |                       |                           | |
| Low risk of HBVr (<1%) | Routine screening not recommended | Not recommended (B2) | Not recommended (B2) | Not applicable | No recommendation (knowledge gap) |
| Traditional immunosuppression |                |                       |                       |                           | |
| Intra-articular corticosteroids |                |                       |                       |                           | |
| Systemic corticosteroids for < 1 wk |                |                       |                       |                           | |
| American Association for the Study of Liver Disease 2009[^110] | Anyone at high risk of HBV infection; Table 1 (II -3) | HBsAg and anti-HBc | Yes (regardless of HBV DNA level) | No recommendation (knowledge gap) | Monitoring recommended; no specific test/frequency provided |
|                        |                        |                |                       |                           | |
|                        |                        |                | Maintain for 6 mo completion of chemotherapy (III) | Lamivudine (I) or telbivudine (III) if the anticipated treatment duration is short (<12 mo) and baseline HBV DNA is not detectable Tenofovir or entecavir if anticipated treatment duration > 12 mo (III) | |

[^80]: Pattullo V. HBV reactivation with chemotherapy
| European Association for the Study of Liver Disease 2012 \(^{[103]}\) | All candidates for chemo- and immunosuppressive therapy (A1) | HBsAg and anti-HBc; HBV DNA if serology + ve | Yes (A1) | Yes if: Lamivudine if HBV DNA < 2000 IU/mL and the treatment duration is short/finite (B1) Entecavir or tenofovir if HBV DNA is high, lengthy or repeated cycles of immunosuppression (C1) | ALT and HBV DNA every 1-3 mo | Regardless of HBV DNA level | HBV DNA detectable |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | | | | | | |
| Asian-Pacific Association for the Study of Liver Disease 2012 \(^{[109]}\) | All patients prior to receiving immunosuppression or chemotherapy | HBsAg (IVA) | Yes | HBV DNA should be closely monitored and treated with nucleos(t)ide analogue when needed (IVA) | | | |
| | | | | | | |
| | | | | | | |
| American Society of Clinical Oncology Provisional Clinical Opinion 2010 \(^{[111]}\) | Advise against routine serological screening. Screen those with High risk of HBV exposure; evidence of liver disease Therapeutic regimen with high risk of HBV including all patients undergoing rituximab therapy Haematopoetic stem cell transplant | HBsAg; anti-HBc if receiving rituximab | Consider role of antiviral therapy No specific recommendation provided | No specific recommendation provided | No specific recommendation provided | Do not delay chemotherapy |

The grade of recommendation and/or level of evidence have been noted where available. AGA and EASL guidelines: evidence grade A: High quality; B: Moderate quality; C: Low quality. Recommendation grade 1: Strong; 2: Weak. AASLD guidelines: II-1: Non-randomised controlled trials; II-2: Cohort or case-control studies; II-3: Case series; III: Expert opinion. APASL guidelines: Quality of evidence ranked from Ⅰ (highest) to Ⅴ (lowest); strength of recommendations ranked A (strongest) to D (weakest). HBV: Hepatitis B virus; HBVr: Hepatitis B virus reactivation; CDC: The Centre for Disease Control; + ve: Positive; - ve: Negative; ALT: Alanine aminotransferase.
and nation to fund the serological testing and manage positive results. Studies evaluating the efficacy and cost-effectiveness of the various screening strategies as relevant to the main global regions are needed.

MONITORING IN ANTI-HBC POSITIVE PATIENTS WHO DO NOT RECEIVE ANTIVIRAL PROPHYLAXIS

The data presented in this review thus far indicate that not all HBsAg negative/anti-HBc positive patients will benefit from antiviral prophylaxis, e.g., patients with undetectable HBV DNA who are prescribed lower potency or limited duration immunosuppressive drug regimes. In those who do not receive antiviral prophylaxis, monitoring for features of HBVr is intuitive, however there is a paucity of data as to how this monitoring should be carried out. There is a general consensus from the international associations that some form of monitoring is required. The EASL recommends ALT and HBV DNA testing every 1-3 mo and treatment upon any evidence of HBVr; but this is based on relatively weak level of evidence (C1, Table 3). An alternative approach may be to test for HBsAg in HBsAg negative/anti-HBc positive patients to monitor for seroreversion, which may occur prior to detection of HBV DNA or ALT rise. The remainder of the major societies do not make specific recommendations owing to the knowledge gap in this area. Further data is required to determine the method, frequency and duration of monitoring. Similar to issues arising regarding screening for HBV, the monitoring for HBVr in patients who do not receive prophylaxis will be guided by the prevalence of HBV and HBVr; cost-effectiveness as well as the access to testing and follow-up that varies across the globe.

MONITORING AFTER THE CESSATION OF ANTIVIRAL PROPHYLAXIS

Some patients who receive antiviral therapy at the initiation of chemotherapy or immunosuppression may need to remain on antivirals long term if there is underlying chronic liver disease and ongoing treatment criteria are met[103,109,110]. In those who receive antiviral prophylaxis without otherwise meeting ongoing treatment criteria for chronic HBV, once the decision has been made to cease antiviral prophylaxis there is no evidence base to guide how monitoring is best performed. The major associations do not make specific recommendations as to how to perform post-prophylaxis monitoring. Measurement of HBV DNA and ALT every 1-2 mo for 3-6 mo after cessation of lamivudine prophylaxis have been proposed[90], but based the observations of many of the aforementioned studies, these patients should be monitored for at least 12 mo, if not, long-term. Furthermore, relapse of the underlying malignancy requiring resumption of chemotherapy would warrant reinstitution of antiviral prophylaxis and should not be overlooked.

A COMPARISON OF THE INTERNATIONAL GUIDELINES ON THE PREVENTION AND MANAGEMENT OF HBVr

The guidelines of the major international associations for the HBV screening, antiviral prophylaxis and monitoring have been referenced, where relevant, throughout this review and are summarised in Table 3, the most recent being the technical review and guidelines of the American Gastroenterological Association[63,60]. It must be noted that some of these recommendations span back to 2009, and as such more recent data would not have been included when older recommendations were made. The application of these guidelines by the clinician warrants consideration of clinical circumstances, resources available and cost-effectiveness, which are patient and region/nation specific.

CONCLUSION

Clinicians managing patients with malignancy need to be vigilant of the potential for HBVr as a complication of chemotherapy in susceptible cases. Those at risk for HBVr must be screened serologically for the virus according to international guidelines, which are based on the best available evidence. Prophylactic antiviral therapy with lamivudine or other nucleos(t)ide analogue should be instituted prior to the start of chemotherapy. Prevention is better than cure.

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