Optimizing antiviral agents for hepatitis B management in malignant lymphomas

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Abstract: The global scale of hepatitis B infection is well known but its impact is still being understood. Missed hepatitis B infection impacts lymphoma therapy especially increased risk of hepatitis B virus (HBV) reactivation and poor treatment outcomes. The presence of undiagnosed chronic hepatitis also undermines chronic HBV screening methods that are based on a positive HBsAg alone. The goal of this review is to evaluate the literature for optimizing antiviral therapy for lymphoma patients with HBV infection or at risk of HBV reactivation. Relevant articles for this review were identified by searching PubMed, Embase, Ovid Medline, and Scopus using the following terms, alone and in combination: "chronic hepatitis B", "occult hepatitis B", "special groups", "malignant lymphoma", "non-Hodgkin's lymphoma", "Hodgkin's lymphoma", "immunocompromised host", "immunosuppressive agents", "antiviral", "HBV reactivation". The period of the search was restricted to a 15-year period to limit the search to optimizing antiviral agents for HBV infection in malignant lymphomas [2001–2016]. Several clinical practice guidelines recommend nucleos(t)ide analogues-entecavir, tenofovir and lamivudine among others. These agents are best initiated along with or prior to immunosuppressive therapy. Additional methods recommended for optimizing antiviral therapy include laboratory modalities such as HBV genotyping, timed measurements of HBsAg and HBV DNA levels to measure and predict antiviral treatment response. In conclusion, optimizing antiviral agents for these patients require consideration of geographic prevalence of HBV, cost of antiviral therapy or testing, screening modality, hepatitis experts, type of immunosuppressive therapy and planned duration of therapy.

Keywords: Hepatitis B; non-Hodgkin lymphoma; malignant lymphoma; antiviral therapy

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Prevalence of chronic hepatitis B (CHB) by region, age group and special groups (lymphoma)

The hepatitis B virus (HBV) is a common human infection which belongs to the hepadnaviridae family. The chronic form of HBV infection is more prevalent than the acute type, and global estimate of chronic cases is 300 million or more (1-3). Despite the likelihood that 95% of adults will recover from an acute HBV infection, impaired viral clearance facilitates complications such as chronic hepatic inflammation, hepatocellular carcinoma and lymphomas (4-7). On a global scale, the mortality from HBV complications is estimated at about 780,000–1 million yearly and adds to existing burdens to health systems (2,8). Global estimates of CHB prevalence indicate high prevalence of CHB in the African and Western pacific region and countries with the highest number of HBsAg-positive individuals include China (74 million), India (17 million) and Nigeria (15 million) (9). Significant decrease in CHB prevalence has been recorded over the last 5 decades especially in countries

located in South East Asia, Western Pacific, and Eastern Mediterranean regions. However, prevalence rates are increasing in parts of Europe partly as a result of migrant influx from highly endemic countries (10,11). In addition, vaccination efforts in parts of Europe are focused on high risk groups rather than the WHO recommendation of universal vaccination of newborns (12). HBsAg prevalence has been consistently low in countries such as Japan, Western Europe, Australia and most countries in the Americas as a result of early vaccination (9).

There are certain groups of patients that will benefit most from screening and monitoring assays of HBsAg, anti-HBc and HBV DNA. This group includes children, pregnant women, patients with acute and fulminant hepatitis B, decompensated cirrhosis, co-existing chronic renal disease, transplant subjects, and cancer patients on chemo-immunotherapy (13-15). These patients are more vulnerable to fatal hepatitis or HBV reactivation and are usually excluded from clinical trials (13,14). They constitute a majority of those with CHB and require concerted research on optimizing antiviral therapy among this group of patients (13,14). Individuals with negative HBsAg assay are not completely free of the risk of reactivation of hepatitis since viral DNA and anti-HBc may persist as an occult hepatitis B infection (OBI) (16-18). Presence of OBI undermines chronic HBV screening methods based on a positive HBsAg alone. Undiagnosed OBI also limits the prescription of antiviral agents that would have benefited this special group of patients in a timely manner. Malignant lymphoma patients are the group of focus in this review because studies have demonstrated an association between HBV and lymphoma etiology, likewise, lymphoma treatment outcomes (7,15,19). In addition, studies have demonstrated hepatitis B viral markers detectable in both Hodgkin's and non-Hodgkin's lymphomas with a propensity for non-Hodgkin's lymphoma, and the diffuse B-cell lymphoma subtype (5,15,20-26).

This review is also critical because lymphoma therapy has evolved rapidly and resulted in improved survival over the last decade (26-28). However, this success in lymphoma therapy is undermined by the influence of chronic HBV on survival outcomes among these patients who tend to be immunosuppressed (29-31). Therefore, lymphoma patients with hepatitis B are a special group of patients that require optimizing HBV antivirals to improve treatment outcomes. The goal of this review is to evaluate the literature for optimizing antiviral therapy for lymphoma patients with HBV infection or at risk of HBV reactivation.

Review criteria

Relevant articles for this review were identified by searching PubMed, Embase, Ovid Medline, and Scopus using the following terms, alone and in combination: "chronic hepatitis B", "occult hepatitis B", "special groups", "malignant lymphoma", "Non-Hodgkin's lymphoma", "Hodgkin's lymphoma", "immunocompromised host", "immunosuppressive agents", "antiviral", "HBV reactivation". Full text articles of all selected studies were retrieved, and if a paper was selected for inclusion, the bibliographic references were scrutinized to identify additional relevant studies. The period of the search was restricted to a 15-year period to limit the search to optimizing current antiviral agents for HBV infection in malignant lymphomas [2001–2016].

Mechanism of HBV infection & chronicity

The liver has numerous functions that include energy metabolism and immunity (32,33). A dysfunction in any of these processes results in metabolic impairment and more importantly, chronic hepatocyte inflammation, lymphomas and hepatocellular malignancies (34). Studies across countries (Asia, Europe, Australia, and United States) have demonstrated a possible causal association between chronic HBV infection and risk of lymphoma with an estimated odds ratio ranging from 1.5–3.6 (5,15,35,36). Once HBV infection occurs with or without evidence of seroconversion, it persists in the body, exposing certain individuals to risk of chronic infection, acute flare, reactivation or fulminant hepatitis (37). The HBV is transmitted through contact with infected blood, semen, and other body fluids; primarily through perinatal transmission from an infected mother, sexual contact with an infected person, sharing of contaminated needles, syringes, or other injection drug equipment, needle sticks or other sharp instrument injuries (38).

Once the virus reaches the body fluids of a new host, the virus invades the susceptible host hepatocytes where it fuses with the cellular membrane and releases its complementary DNA (cccDNA) for replication in the hepatocyte nucleus. Transcription occurs in a reverse manner with negative strand synthesis preceding positive strand synthesis. Subsequently, the virion receives its coat protein (HBsAg) in the cytoplasm before budding and secretion into the host blood (39,40) (*Figure 1*).

Key step that have been targeted in the viral replication process is the reverse transcription phase where viral

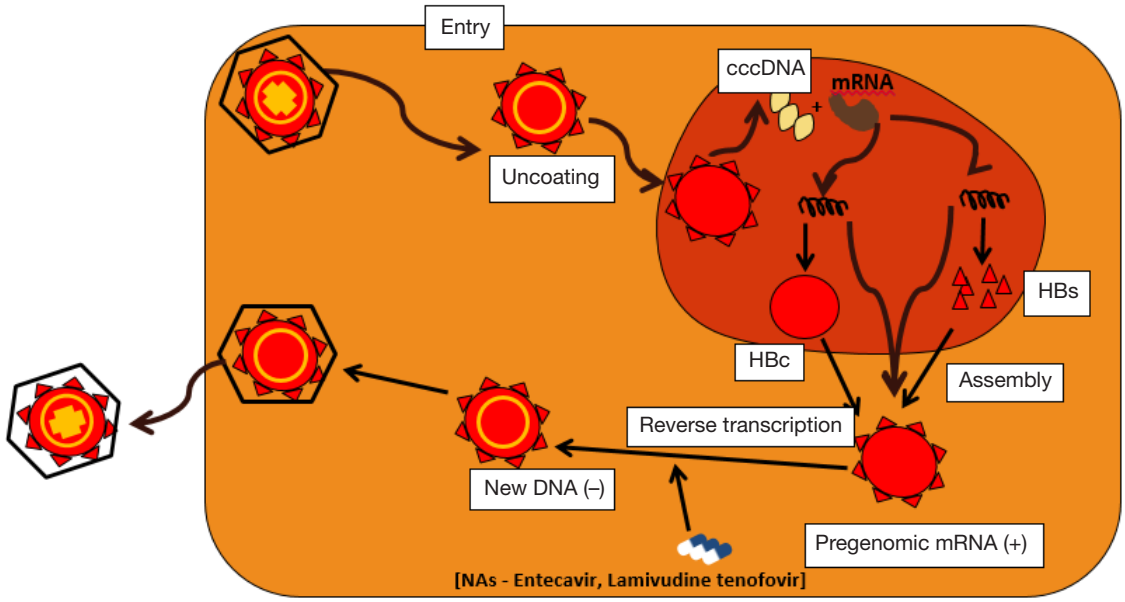

Figure 1 Hepatitis B virus (HBV) pathogenesis and drug targets.

maturation and replication is inhibited. Novel agents are undergoing clinical trials to target cccDNA which tends to persist in host, largely accounting for chronicity (39,40). Evolution in the understanding of the viral replication process continues to drive development of current and novel antivirals in different phases of clinical trials.

Diagnosis of CHB and parameters

It is important to make a clear distinction among viral markers used to aid diagnosis of CHB infection and its variants such as OBI. Markers of acute or CHB in a susceptible host include HBsAg and anti-HBs, HBeAg and anti-HBe, and anti-HBc IgM and IgG, HBV DNA (41); the presence of any of this signifies important physiological or disease states. Acute infection is indicated by presence of antigens, HBsAg and/or HBeAg, followed by the antibody, anti-HBc IgM. Early convalescence is indicated by the antibody, anti-HBc IgM which is cleared out in most patients. Late convalescence is indicated by elevated anti-HBc IgG or anti-HBs. Convalescence may then transit into chronicity which is confirmed by persistently elevated titers (≥6 months) of anti-HBc IgG, HBsAg, and or anti-HBe. Currently available serological assays now utilize HBV DNA levels to diagnose occult HBV, HBV reactivation in lymphoma chemo-immunotherapy (or cancer immunotherapy), HBV resistance during antiviral therapy, or HBeAg seroconversion during chronic HBV (accompanied by a sudden increase in serum ALT and HBV DNA) (*Table 1*).

Occult HBV infection

The chronic form of HBV infection is facilitated by the persistence of covalently closed circular DNA (cccDNA) (42). The term occult HBV infection represents the absence of detectable serum HBsAg (resolved HBV infection) following immune-mediated control of viral replication but persistent viral genomes in the liver (43). The occult form of HBV emerges following a progressive disappearance of the hepatitis surface antigen over the years post-infection (43). The European Association of Liver Disease [2008] endorsed the definition of occult HBV as the presence of HBV DNA in the liver of individuals testing HBsAg-negative using currently available assays (16). When detectable, the amount of HBV DNA in the serum is usually very low (<2,000 IU/mL) (44,45). Occult HBV is clinically relevant considering silent transmission routes such as during blood transfusion, hemodialysis, organ transplant or potential reactivation during immunosuppressive therapy (43,46-48). Other factors that affect the natural history of CHB include host factors (gender, age at infection, family history), viral factors (viral mutation, genotype and HBV DNA level), and environmental factors (co-infection with hepatotrophic

Table 1 Serologic markers and differential diagnoses associated with hepatitis B virus (HBV) infection in lymphoma patients

Diagnosis	Markers
HBV infection phases	
Acute infection, window period	HBsAg and/or HBeAg, followed by, anti-HBc IgM
Early convalescence	Anti-HBc IgM
Late convalescence	Anti-HBc IgG or anti-HBs
Chronic infection	Persistently elevated titers (≥6 months) of anti-HBc IgG, HBsAg, and or anti-HBe
Occult HBV	HBsAg-negative. when detectable, the amount of HBV DNA in the serum is usually very low (<2,000 IU/mL)
HBeAg seroconversion during chronic HBV	Sudden increase in serum ALT and HBV DNA)
HBV reactivation	
HBV reactivation in lymphoma chemo-immunotherapy	HBV DNA ≥20,000 IU/mL with no baseline HBV DNA or;
	Newly detected HBV DNA level of ≥100 IU/mL with previously stable or undetectable levels or;
	Elevated HBV DNA ≥2 $\log_{10}$ IU/mL in patients with detectable HBV DNA at baseline or;
	≥10-fold increase in HBV DNA compared with baseline
Antiviral treatment response	Suppression in HBV DNA level to <3 $\log_{10}$ IU/mL is an objective evidence
HBV resistance during antiviral therapy	Elevated HBV DNA while on antiviral therapy for HBV especially previously untreated patients on lamivudine or previously treated patients on entecavir
Differential diagnosis of HBV	
Alcoholic hepatotoxicity, radiation and other medications	HBV DNA is usually not elevated
Liver metastasis, sepsis, acalculous cholecystitis or hepatic veno-occlusive disease	
Presence of hepatotoxic agents such as viruses	Elevated aminotransferase with viral markers of hepatitis A, C, D, E, cytomegalovirus or herpes viruses in the immunocompromised

viruses, parasites or toxins) (49). Currently, there is no standard screening method for occult HBV infection except testing HBV PCR/DNA in high risk patients, neither does any society recommend HBV DNA screening for low risk patients at the current time.

HBV in lymphoma patients

Lymphoma patients are at risk of HBV reactivation due to a number of factors but individuals with inactive or occult forms of HBV are at greater risk of reactivation. One factor is lymphomagenesis which provides a milieu of immunosuppression which favors HBV replication. In addition (50,51), when immunosuppressive agents are initiated in lymphoma, induced immunosuppression triggers viral replication that manifests as HBV reactivation (38,52-54). It is important to note that spontaneous reactivation can occur in individuals without lymphoma, especially individuals with positive HBeAg, likewise co-infection with HIV, bacterial infections or stressors (emotional and physical) (55). A common underlying mechanism is the role of altered patient immune response (55). Heredity or acquired genetic mutations also play a critical role in HBV marker persistence, response to antiviral therapy and risk of NHL (20,56-60). Case-control studies among European patients with NHL have demonstrated that individuals with dysfunction in WBC telomere length have a higher risk of B-cell lymphoma (61-63). Among patients with lymphoma and concurrent HBV reactivation, a key environmental factor includes specific drug classes. These drugs include

chemotherapeutic agents, with or without combination of anti-CD20 agents, anti-CD52 agents, immunosuppressive (methotrexate or azathioprine) or glucocorticoids (64-68). Additional biologic agents such as TNF inhibitors and tyrosine kinase inhibitors have been linked to HBV reactivation but are not in use for lymphoma therapy currently.

Risk stratification of HBV reactivation

The general classification of HBV reactivation is based on HBV biomarkers, type of immunosuppressive therapy and/or use of glucocorticoid combined therapy (64-70). Among patients with a positive HBsAg or anti-HBc biomarkers, a very high risk of HBV reactivation (>20%) is associated with anti-CD20 monoclonal antibody agents (rituximab, obinutuzumab, ofatumumab) (37,50,64-68,71-73). The risk may be higher with the presence of HBeAg and/or elevated baseline HBV DNA (74-76). When HBsAg-positive patients are to receive high-dose glucocorticoids (>20 mg/day for ≥4 weeks), they are considered at high risk for reactivation (11–20%). Moderate risk (1–10%) is present where a patient is HBsAg positive and is going to be placed on cytotoxic therapy such as cyclophosphamide, doxorubicin, vincristine, excluding glucocorticoids. Low risk patients (<1%) includes two types of patients: HBsAg-positive patient who is going to receive either methotrexate or azathioprine; HBsAg-negative and anti-HBc-positive patients going to receive high-dose glucocorticoids or anti-CD52 agent, alemtuzumab (77). The risk for reactivation is lowest for HBsAg negative and anti-HBc-positive patients receiving non-glucocorticoid-based chemotherapy, azathioprine or methotrexate (77).

Clinical features of reactivation

Most cases of HBV reactivation do not have symptoms and the only indicator is an elevated HBV DNA level (76,78,79). Fewer patients with HBV reactivation may present with increased aminotransferase levels, with or without mild features such as nausea and vomiting. Grave clinical features include icterus, decompensated hepatic function, or mortality, especially with existing cirrhosis (53,56,80).

Serology of HBV reactivation and differential diagnoses in lymphoma patients

In order to make a diagnosis of HBV reactivation, there should be serologic evidence of HBV (71,81):

- HBV DNA ≥20,000 IU/mL with no baseline HBV DNA or;
- Newly detected HBV DNA level of ≥100 IU/mL with previously stable or undetectable levels or;
- Elevated HBV DNA ≥2 $\log_{10}$ IU/mL in patients with detectable HBV DNA at baseline or;
- ≥10-fold increase in HBV DNA compared with baseline.

When making a diagnosis of HBV reactivation it is crucial to differentiate reactivation from the following conditions: acute HBV (elevated IgM anti-HBc titer), HBeAg seroconversion during chronic HBV (accompanied by a sudden increase in serum ALT and HBV DNA), HBV resistance (elevated HBV DNA while on antiviral therapy for HBV especially previously untreated patients on lamivudine or previously treated patients on entecavir), presence of hepatotoxic agents such as viruses (elevated aminotransferase with viral markers of hepatitis A, C, D, E, cytomegalovirus or herpes viruses in the immunocompromised). Clinical manifestation of hepatitis may be present in other conditions such as alcoholic hepatotoxicity, radiation and other medications but HBV DNA is usually not elevated. Lastly, other liver diseases need to be ruled out in lymphoma patients and these include liver metastasis, sepsis, acalculous cholecystitis or hepatic veno-occlusive disease (77).

Antivirals in CHB and lymphoma

There are currently two treatment modalities for chronically infected HBV patients that include nucleot(s)ide analogs and interferon alpha. Interferons are not currently prescribed for lymphoma patients with HBV reactivation because of the associated intolerance, adverse reactions and selective effectiveness (40). The majority of infected patients require lifelong therapy, yet viral rebound commonly occurs following termination of therapy. Nevertheless, antivirals are recommended for all lymphoma patients with HBV reactivation and those with acute HBV or infection from other hepatotropic viruses. The focus of this review is solely on optimizing antiviral therapy for HBV among patients with lymphoma; therefore, other differential diagnoses enumerated above will require extensive workup to determine a suitable therapy.

Drug targets in viral infection cycle/phase

The reverse transcription phase of the viral life cycle

in susceptible hosts is the most successfully targeted phase. The reverse transcriptase enzyme synthesizes double stranded DNA (dsDNA) from host RNA, and the synthesized dsDNA integrates into the host genome. The nucleos(t)ide analogs are taken up by hepatocytes, converted by viral and cellular enzymes to a form which competitively block nucleotide binding to reverse transcriptase, and polymerase enzymes (DNA/RNA), thereby terminating normal DNA chain formation. Lamivudine requires phosphorylation while tenofovir requires phosphorylation to be activated. The result of the blocking action is prevention of virion assembly and maturation. Lamivudine and Tenofovir are the main antivirals in use in HBV infection or reactivation. Non-nucleos(t)ide polymerase inhibitors bind the reverse transcriptase site at a different site from nucleoside reverse transcriptase inhibitor (NRTI) and also prevent viral maturation and release.

Antiviral therapy for lymphoma patients with HBV also target the reverse transcription phase of the viral life cycle thereby limiting viral maturation and replication (*Figure 1*). More importantly, currently available antiviral therapies do not target defective responses of the immune system or the persistence of covalently closed circular DNA (cccDNA) in the infected hepatocytes. Thus, developing different approaches to achieve sustained cure or elimination of HBV is urgently needed.

Guidelines & summary of evidence for effective antiviral agents in lymphoma patients

Several clinical practice guidelines recommend nucleos(t)ide analogues entecavir, tenofovir and lamivudine among others. These agents are best initiated along with or prior to immunosuppressive therapy. The timing and choice of therapy depends on the level of risk, planned duration of chemotherapy, HBV-DNA level, and prior antiviral therapy (82-87). High risk patients ought to receive antiviral therapy preferably before or simultaneously with potent immunosuppressive agents. Entecavir and tenofovir are first line agents according to most studies and guidelines (55,82,85,86), however, lamivudine may be used if chemotherapy will last less than 6 months, HBV-DNA (<2,000 IU/mL), the patient is treatment-naïve and first line agents are impossible to obtain (55,82,84,88). For patients with prior lamivudine therapy, tenofovir may be more suitable than entecavir after determining HBV resistance (37,89). Patients determined to be at lower risk would suffice on close monitoring of HBV DNA levels instead of preventive antiviral therapy.

Antiviral therapy should continue for at least 6 months post-chemotherapeutic agents and extended to a minimum of 12 months when the anti-CD20 agent, rituximab is administered (82,85,86). Suppression in HBV DNA level to <3 $\log_{10}$ IU/mL is an objective evidence of antiviral treatment response and may be an appropriate time to initiate immunosuppressive agents among patients with significantly elevated HBV DNA (37,88).

First-line therapy for chronic HBV in lymphoma patients is predominantly entecavir, tenofovir and lamivudine, yet, the optimal workup for individual patients differ. Some guidelines now support inclusion of hepatitis specialists in managing these patients (84,89). Additional methods recommended for optimizing antiviral therapy include laboratory modalities such as HBV genotyping, timed measurements of HBsAg and HBV DNA levels to measure and predict antiviral treatment response (55,82,85,87,88,90).

Conclusions

Lymphoma patients are special groups of individuals at risk of adverse outcomes from co-existing HBV infection. All lymphoma patients do not carry the same level of HBV reactivation risk from exposure to immunosuppressive agents. Lymphoma patients on rituximab therapy and are positive for HBsAg have the highest risk of HBV reactivation. First line antiviral agents recommended include entecavir, lamivudine and tenofovir. Optimizing antiviral agents for these patients require consideration of geographic prevalence of HBV, cost of antiviral therapy or testing, screening modality, hepatitis experts, type of immunosuppressive therapy and planned duration of therapy. A minimum period of 6 months is recommended for antiviral therapy but the time to stop therapy is unclear. Lastly, efforts to increase CHB screening and therapy need to be sustained to improve treatment outcomes for lymphoma patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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