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Holistic Integrative Oncology (2023) 2:38
https://doi.org/10.1007/s44178-023-00061-w

Holistic Integrative Oncology

REVIEW

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Hepatitis B virus–associated diffuse large B cell lymphoma: epidemiology, biology, clinical features and HBV reactivation

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Abstract

Diffuse large B cell lymphoma (DLBCL) is the most common type of lymphoma in adults with high heterogeneity. Recent studies have manifested that the occurrence and development of DLBCL is related to hepatitis B virus (HBV) infection. As a medium-to-high prevalence area of HBV infection in China, the importance and exact mechanism of HBV infection in the occurrence of DLBCL have attracted considerable attention. HBV-associated DLBCL has unique clinical characteristics, poor treatment effect and inferior prognosis. HBV reactivation caused by DLBCL treatment also needs for constant vigilance. In this review we summarize the current research progress in the epidemiology, pathogenesis, clinical characteristics, HBV reactivation and antiviral therapies of HBV-associated DLBCL, in order to provide reference for clinical diagnosis and treatment.

Keywords Hepatitis B virus, Diffuse large B cell lymphoma, HBV reactivation

1 Introduction

Non-Hodgkin lymphoma (NHL) is a main type of hematological lymphatic malignancy, which accounts for about 3% of newly diagnosed cancer cases worldwide. DLBCL, as the most frequent subtype of NHL in adults, accounting for approximately 30% of NHL, and its incidence is increasing annually [1]. HBV is a spherical deoxyribonucleic acid virus with hepatocellular and lymphotropic characteristics, which has been a threaten to global public health security with 316 million people around the world experienced chronic HBV infection (CHB) [2]. Sufficient evidences have demonstrated an increased risk of DLBCL in patients with CHB. Meanwhile, patients with lymphoma have a higher incidence of HBV infection than in the general population and patients with solid tumors other than primary hepatocarcinoma. HBV-associated DLBCL has unique clinical features and poor prognosis. In addition, although currently effective immunochemotherapy significantly improves the prognosis of DLBCL, treatment with DLBCL can lead to adverse clinical outcomes due to HBV reactivation. Prophylactic application of antiviral agents can effectively reduce the incidence and mortality of HBV reactivation. On account of above considerations, here we review the progression on HBV-associated DLBCL from aspect of epidemiology, pathogenesis, clinical features, HBV reactivation and antiviral therapies, so as to deepen the understanding of HBV-associated DLBCL and provide reference for clinical practice.

1.1 Characteristics and epidemiology of HBV infection and NHL

1.1.1 HBV

HBV belongs to the hepatotropic DNA virus family and is composed of incomplete circular double-stranded DNA. The HBV genome contains four partially overlapping open reading frames, which are S, C, P and X regions respectively [3]. The S region is further divided into three

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coding regions: pre-S1, pre-S2 and S, which encode pre-S1 protein, pre-S2 protein and HBsAg on the envelope respectively. C region is divided into preC and C regions, encoding HBeAg and HBcAg separately. The P region encodes HBV DNA polymerase which is involved in viral replication [4]. The transactivating HBxAg encoded in the X region can activate various regulatory genes of HBV itself to promote HBV replication. After suffering from chronic infection, HBV sustains a steady covalently closed circular DNA (cccDNA) pool by intracellular HBV genomic cycling and secondary infection, makes it difficult to completely eliminate HBV [5, 6].

HBsAg is a marker of present HBV infection and chronic HBV infection can be diagnosed if serum HBsAg is continuously positive for 6 months. Chronic hepatitis B virus remains a global health challenge affecting more than 2 billion people with high liver-related morbidity and mortality worldwide [7]. World Health Organization reported that 80% of the 292 million HBsAg carriers are concentrated in 21 countries, among which China, India, Nigeria, Indonesia and the Philippines account for 57% of the total number of infected people [8]. A meta-analysis of data from the HBV epidemiological survey in China estimated that the prevalence rate of HBV infection of the general population in China from 2013 to 2017 was 6.89% (95%CI :5.84–7.95%). As of 2018, there were about 84 million HBsAg carriers in China [9]. Although the overall prevalence of HBV in China has declined over the past two decades due to the popularity of hepatitis B vaccines, the absolute number of people infected is quite huge. Previously HBV was deemed to be the main pathogenic factor leading to liver cirrhosis and hepatocellular carcinoma (HCC). For the past few years, increasing epidemiological evidences have indicated a significant association between HBV infection and DLBCL.

1.1.2 DLBCL

DLBCL is an aggressive lymphoproliferative malignancy derived from mature B cells with highly heterogeneous. As the leading type of adult NHL, DLBCL accounting for about 30-40% of all NHL cases, with over 150,000 DLBCL newly diagnosed annually around the world [1, 10]. The pathogenic factors of DLBCL are still unclear. At present, the identified factors mainly include genetic characteristics, immune disorders, viral infections, environmental and occupational exposures. According to the gene expression profile, DLBCL can be further divided into activated B cell-like (ABC) subtypes and germinal center B-cell (GCB) subtypes with different chromosomal alterations and clinical outcomes [11]. About 70% of DLBCL patients are in the advanced stage of the disease at first diagnosis and typical clinical performances of DLBCL contain fever, night sweats, weight loss, painless lymphadenopathy, accompanied with corresponding symptoms related to specific tumor sites. With the application of the targeted drug rituximab, the treatment of DLBCL has achieved breakthrough progress and the 10-year overall survival rate has increased to 44%. Nowadays, R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) is the standard first-line treatment for newly diagnosed DLBCL, but there is still an unmet need for treatment [12]. Approximately 50–60% of patients are cured by R-CHOP regimen, while the remaining 40% have poor response to treatment. Treatment of patient with high risk (age > 60, high IPI score, non-GCB, MYC/BCL-2 double expression or gene rearrangement) is intractable, while R-CHOP regimen is insufficient to cure, thus personalized treatment is required. For young patients with high risk, intensive immunochemotherapy can improve the efficacy and first-line autologous hematopoietic stem cell transplantation (ASCT) may further improve disease-free survival. Reduced immunochemotherapy may be considered for elderly and frail patients. For relapsed and refractory patients, CD20/CD3 bi-specific antibodies mosunetuzumab, odronextamab and CD19 CAR-T therapy are expected to bring more benefits in recent years [13–15].

1.2 Association between HBV infection and DLBCL

1.2.1 Increased incidence of DLBCL in HBV-effected patients

Although the exact etiology of DLBCL has not been elucidated, considerable evidences have accumulated on the association between HBV infection and DLBCL. Current studies have shown that the pathogenesis of DLBCL is closely related to viral infections, such as Epstein-Barr virus, human immunodeficiency virus, hepatitis B virus etc. [16]. As early as 1994, Galun [17]et al. proposed that HBV infection may play a role in hematopoietic cytogenesis and lymphatic malignancy. HBV-infected individuals had a significantly increased risk of NHL (sOR: 2.52; 95% confidence intervals [CI]: 2.22–2.86). while B-cell NHL is more strongly associated with HBV infection than T-cell NHL [18, 19]. HBV can infect and replicate in lymphocytes which has been shown to contribute to DLBCL progression. A study in Taiwan included 203,031 lymphoma patients with the median follow-up of 7–9 years. and found that the incidence of lymphoma in the cohort with chronic hepatitis B was significantly higher than in HBV negative group (29.4/100,000 person-years vs. 15.9/100,000 person-years, $P < 0.0001$). HBV infection was an independent risk factor in NHL, especially in DLBCL (HR: 2.69%,95%CI:2.05–3.52, $P < 0.0001$) [20]. The Korean Cancer Prevention Study conducted a 14-year follow-up found that HBsAg positivity was associated with increased risk of diffuse large B-cell lymphoma ($n = 325$, incidence 6.86 vs. 3.79 per 100,000

person-years; adjusted HR 2·01, 1.48–2.75) but not associated with neither follicular lymphoma, T-cell NHL, nor Hodgkin's lymphoma [21]. A study based on the SEER database to assess the association between HBV infection and various tumors in American elderly population over 66 years of age found that HBV infection was positively associated with the prevalence of DLBCL(adjusted odds ratio [aOR] = 1.24; 95% CI = 1.06–1.46) [22]. Taken together, it has been well documented that HBV infection act as a causative role in DLBCL.

1.2.2 High HBV infectious rate of DLBCL lymphoma

Additionally, the prevalence of hepatitis B infection was higher in lymphoma patients. The positive rate of HBsAg in DLBCL population was 25-61%, significantly higher than the general population(7%) [23]. HBV infection was detected nearly 2.5 times more frequently in lymphoma patients than in controls, indicating that NHL patients were 72% more likely to encounter HBV infection versus controls [24]. The prevalence of HBV infection was higher in patients with B-cell subtype NHL (30.2%) than in patients with other cancers (14.8%; OR:2.6; 95% CI : 2.0-3.4), however, no significant difference was observed in T-NHL. In B-cell NHL, the onset of disease was significantly earlier in patients infected with HBV than in those not (9.5 years) [25]. Chen [23] et al. found that the prevalence of HBV infection was higher in patients with B-cell NHL (23.5%) than in patients with solid tumors (15.6%, $P=0.001$), especially in patients with DLBCL. In recent years, attention has been paid to the relationship between DLBCL and occult HBV infection. Occult hepatitis B infection (OBI) refers to the presence of replicative HBV DNA in the liver and the presence or absence of HBV DNA in the blood while serum HBsAg is negative. Among HBsAg negative patients, the prevalence of OBI in B-cell NHL patients (6%) was higher than that in solid tumor patients and healthy volunteers ($P=0.005$), further supporting the etiological role of HBV in B-cell NHL. Taken the correlation between HBV and DLBCL into account, it is necessary to gain insight into the mechanism of HBV-DLBCL interaction and the unique characteristics of HBV-associated DLBCL.

1.2.3 Interaction mechanism between HBV and DLBCL

The interaction mechanism between HBV and DLBCL has not been fully elucidated. Currently, HBV is considered to affect the development of lymphoma through chronic antigenic stimulation or HBV direct infection of B lymphocytes resulting in immune disorders.

1.2.4 Chronic antigenic stimulation

In the study of the mechanism of hepatitis virus-induced lymphomagenesis, researchers first made a breakthrough in the hepatitis C virus (HCV). HCV envelope protein 2 (E2) is the main anti-HCV target of human B cells. HCV-E2 stimulates polyclonal activation of B cells through antigen stimulation or CD81 binding on the surface of B cells, leading to lymphomagenesis [26, 27]. In analogy to classical antigen-driven HCV-associated lymphoma, the chronic antigen stimulation hypothesis suggests that sustained HBV antigen stimulation induces B cell receptor (BCR) activation, which affects B-cell signaling and promotes abnormal lymphocyte proliferation, leading to lymphoma formation. HBV-associated DLBCL is more likely to be characterized by frequent involvement of the spleen and retroperitoneal lymph nodes [28], which seems to support the notion of chronic antigenic stimulation. DLBCL expresses the immunoglobulin variable heavy chain region (IGVH) gene in the form of BCR, which not only serves as a clonal marker but also provides a source of clues for malignant B cells. *Deng* [28] et al. found that almost all (45/47, 96%) amino acid sequences of the heavy and light chain complementary determining regions 3 in HBsAg-positive DLBCL patients were highly homologous to HBsAg-specific antibodies. It was proposed that HBV-associated DLBCL may originate from B cells selected by HBV antigen through chronic antigenic stimulation. The analysis of immunoglobulin gene hypermutation has enhanced the understanding of various B cells and their tumorigenesis and development. The BCR component of HBV-positive DLBCL appeared to be highly restricted to viral antigens and displayed somatic hypermutation (SHM) burden, suggesting that HBV-associated DLBCL was transformed from HBV antigen selected B cells. It is proposed that HBV-associated DLBCL may originate from B cells selected by chronic antigen stimulation. Moreover, there was no correlation between HBV and DLBCL observed in sporadic infections or vaccinations, implicating a demand for sustained antigen exposure during transformation procedure [29, 30]. Chronic HBV antigen stimulation generated $CD21^{-}CD27^{-}$ atypical memory B cells (atMBCs) with impaired function. AtMBCs entering the germinal center were repeatedly exposed to activation-induced cytosine deaminase (AID)-mediated aberrant SHM, and the accumulation of missense mutations led to B cell clonal proliferation and phenotypic changes of B cells, ultimately resulting in a malignant phenotype and immune escape of memory B cells [31, 32]. Sustained viral antigen stimulation drives immune cell failure and affects the tumor immune microenvironment (TIME). HBV infection led to enrichment of regulatory T cells (Treg) and CD8 + resident memory T cells in TIME, which not only induces epigenetic reprogramming of CD8 + T cell gene regulation and reduced expression of cytokines and effector molecules, but also enhance the expression of suppressor

receptors, such as programmed cell death protein (PD1) [33]. HBV infection caused HBsAg-specific B cells and global B cells to accumulate atMBCs and exhibit abnormal signaling, homing, product antiviral as well as pro-inflammatory cytokines (CD11c and CXCR3), and express high level of inhibitory receptors, which on the one hand affect the body's ability to fight viruses and on the other hand can cause abnormal B cells to develop an immune escape phenotype. These aberrant biological behaviors can be partially rescued by PD-1 blockade, but the role of atMBCs in HBV-associated DLBCL needs to be further investigated [34, 35].

However, *Ren* [36] et al. did not find any significant sequence homology between the CDR3 region and HBsAg or HBsAg-binding proteins in HBsAg + DLBCL patients by immunoglobulin heavy chain gene sequence analysis and there was no biased usage of the IGVH gene. The pathogenic mechanism of HBV-associated lymphoma is an antigen-independent mechanism, which challenges the chronic antigen-stimulation hypothesis. Combined with current research advances and the clinical reality that HBV-associated DLBCL is unresponsive to antiviral therapy, the chronic antigen stimulation model does not appear to fully reveal the potential mechanisms of HBV action in DLBCL.

1.2.5 HBV directly infects B lymphocytes

HBV is a lymphocytic virus, in vitro experiment confirmed that HBV antigen and nucleic acid can be detected in B lymphocytes after HBV infection. In vivo, post-infected B cells internalize the virus into the lymphatic system and store HBV in the lymph nodes as reservoir for a long time. Possible mechanisms of HBV infection of B cells leading to lymphomagenesis include (i) human apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC) family mediating abnormal somatic high frequency mutations (ii) HBV genome integration into host genes driving oncogenic mutations [37, 38].

APOBEC promotes SHM The APOBEC family is a catalytic class of peptides that specifically catalyze cytosine to uracil (C> U) in the genome and are involved in the intrinsic immunity and antiviral responses. Eleven members of the APOBECs family have been identified, including APOBEC1 (A1), APOBEC2 (A2), APOBEC3A-H (3A, 3B, 3C, 3D, 3E, 3F, 3H), APOBEC4 (A4), and AID. Among them, APOBEC3 and AID are the main immunologically active members of the family. APOBEC3 can efficiently inhibit the replication process of many retroviruses and has significant antiviral intrinsic immune activity. Under chronic inflammatory conditions, abnormal expression of the APOBEC family drives genomic mutations. Clustered somatic mutation analysis identified 76.1% of "kataegic" (longer strand-coordinated events in clustered single base substitutions) mutational events in cancer genome were related to AID and APOBEC3 family. AID, an important member of APOBEC family, mediates enhanced gene mutations when B cells are highly activated due to chronic infection, which in turn induces recurrent somatic mutations or structural variants affecting apoptosis, BCR and NF-κB signaling, epigenetic modifications, build a bridge to inflammation-cancer transition [39–41]. In DLBCL, APOBEC can induce TP53 mutation, promote cell proliferation and doxorubicin resistance [42]. In HBsAg + DLBCLs, the total mutation burden of the whole genome was higher and showed more non-silent mutations. Genomic and proteomic analysis of Chinese DLBCL patients revealed 14 preferential mutations in HBsAg + DLBCL genome, including KLF2, TMSB4X, CD70, BCL6, FAS, TNFRSF14, UBE2A, CD58, SGK1, ZFP36L1, CXCR4, FOXO1, CSK and MSL2, of which 11 genes are potential off-target genes for AID. It was hypothesized that AID-mediated aberrant SHM may lead to a unique mutational profile in HBsAg + DLBCLs. Multiple alternations of BCL6 such as splice mutations and chromosomal translocations after HBV infection deregulated the transcriptional repression of the proto-oncogene BCL6 thus promote DLBCL development. Among the above mutated genes, the changes of BCL6, CXCR4, KLF2 and SGK1 genes were closely related to FOXO signaling pathway, which regulated the formation of germinal dark region and affected immune activation and BCR signaling pathway [36, 43].

Genomic integration driving oncogenic mutations The integration of HBV DNA into the host genome is thought to be an important factor in the development of HBV-associated DLBCL, however, the exact mechanism is not fully understood. HBV DNA sequences integrate into the host induces genomic instability and disrupts oncogenes, thereby promoting tumorigenesis. Identification of HBV DNA integration sites in NHL and comparison of HBV DNA integration patterns between NHL and HCC revealed that HBV DNA in NHL repeatedly targets seven protein-coding genes, including ANKS1B, CAPZB, CTNNA3, EGFLAM, FHOD3, HDAC4, and OPCML, that may have potential functions in the development of NHL. Six non-coding RNA moieties, namely LINC00499, LINC00603, LINC01360, LINC00486, MIR7976 and PWRN1, were also targeted and integrated by HBV DNA repeatedly. Among them, LINC00486 intron 4 was repeatedly targeted twice by HBV DNA in NHL and 10 times in HCC, suggesting a common insertional mutagenesis mechanism in HCC and NHL. Gene Ontology analysis revealed that the 406 HBV-targeted genes in

NHL were significantly enriched in NHL developmental processes and pathways related to cell differentiation, signal transduction, cell junctions and transcriptional regulation. ($P < 0.05$), suggesting a potential role of HBV genomic integration in the development of DLBCL [44].

As aforementioned, HBx has a broad range of transcriptional activation functions and non-specific transactivation effects [3]. The integrated viral sequences promote tumorigenesis by producing truncated and mutated HBx proteins, disrupting cellular control programs or activating oncogenic signaling to promote tumor development [45, 46]. The HBx antigen positivity rate in $HBsAg^+$ DLBCL patients was 48.9%. HBx expression was significantly correlated with high levels of c-Myc expression and poor response to treatment [47]. Besides, HBx protein upregulates lncNBAT1 expression and induces resistance of DLBCL cells to chemotherapeutic agents (methotrexate or cytarabine) that induce S-phase block by inhibiting APOBEC3A expression through interaction with STAT1 [48]. The HBV + DLBCL microenvironment was significantly enriched with a set of memory B cells highly expressing the HBx-targeted genes EGR2 and EGR3, which were presumably associated with poor prognosis in HBV-associated DLBCL patients [49]. Furthermore, HBx can be directly involved in the regulation of p53 and NF-κB signaling pathways, as well as the regulation of transcriptional networks [36].

1.2.6 Immune disorder

HBV infection activates cytoimmunity and humoral immunity, followed by the production of various inflammatory factors that remodel the TIME causing immune dysfunction, leading to immune tolerance and immune surveillance deficiency, resulting in clonal proliferation of lymphocytes and lymphomagenesis. Single-cell level analysis of HBV-associated DLBCL tumor cells and tumor immune microenvironment cells revealed that the expression of major histocompatibility complex II (MHC-II) molecules in GCB subtype HBV-associated DLBCL was absent and promoted the immune escape of tumor cells. Tumor cells of ABC subtype HBV + DLBCL, although highly expressing MHC-II molecules, received more antiproliferative signals from CD4 + T cells through the CD40LG-CD40 axis to stimulate tumor cell growth. There was also a large enrichment of Tregs in the ABC subtype, providing the possibility of immune escape. HBV infection causes significant negative effects on both tumor cells and microenvironmental cells, leading to poor prognosis in DLBCL [36, 49]. Antigen-presenting dendritic cells (DCs) play an important role in triggering primary antiviral responses and sustained immune responses. Impaired immune responses to HBV-encoded antigens in CHB are associated with defective DC function [50]. HBV infects hematopoietic stem cells, inhibits their proliferation and differentiation into DCs, downregulates their effector immune phenotype leading to immune tolerance [51]. In addition, the immune system inevitably kills and destroys lymphocytes during HBV clearance. Lymphocytes can proliferate malignantly during the repair process eventually leading to lymphoma.

To sum up, the occurrence and development of HBV-associated DLBCL is a multi-molecular, multi-signaling pathway interweaving and multi-step process. The specific mechanism needs to be further explored.

1.2.7 Clinical features and prognosis of HBV-associated DLBCL

Accumulated evidence has indicated that HBV-associated DLBCL patients have unique clinical features, unsatisfactory response to treatment and poor prognosis. *Deng* [28]et al. reported that HBsAg-positive DLBCL patients had younger median age of onset, higher international prognostic index (IPI), later disease stage, more common retroperitoneal lymph node and spleen involvement than counterpart. *Ren* [36]et al. analyzed the clinical data of 275 Chinese DLBCL patient, and found that HBsAg + DLBCL were younger, more advanced at diagnosis, and had worse outcome. In DLBCL, especially in relapsed and refractory patients, the objective response rate was lower in HBsAg positive group [52].

Numerous studies have shown that HBsAg positivity is an indicator of inferior prognosis in DLBCL. The progression free survival (PFS) and overall survival (OS) of HBsAg-positive patients were worse than those of HBsAg-negative group, with 2y PFS of 36% vs. 61% and 2y OS of 47% vs. 70%, respectively [28]. Another study demonstrated the 3-year PFS and OS rates of HBsAg-positive and/or HBcAb positive DLBCL were 52% and 77%, severally, while the 3-year PFS and OS rates of HBsAg-negative combined with HBcAb negative DLBCL patients were 76% and 93%, respectively. *Chen* [53] and *Liu* [54] et al. identified HBsAg as an independent prognosis of DLBCL. However, several studies have discovered that HBsAg status did not show significant correlation with DLBCL prognosis [55, 56]. To resolve this controversy, further verification in large prospective studies is required.

1.3 HBV-associated DLBCL and HBV reactivation

1.3.1 Definition and clinical manifestations of HBV reactivation

The natural course of HBV infection is determined by the interaction between viral replication and the host immune response. The natural history of HBV can be divided into four phases: immune tolerance phase,

immune clearance phase, inactive or low (non) replication phase and reactivity phase. HBV DNA is still present in hepatic tissue of inactive or low (non) replication stage patients therefore HBV can reactivate. "Reactivation" means that HBV moves from a "latent infection" state to an active replication state due to immune status changes. At present, there is no uniform international standard for the definition of HBV reactivation. Japanese experts suggested that HBV reactivation be defined as: HBV DNA exceeding 10 times the baseline level in HBsAg-positive patients; serum HBeAg conversion to positive for HBeAg-negative patients; serum HBsAg conversion to positive for HBsAg-negative patients; and serum HBV DNA measurable for patients with undetectable baseline HBV DNA [57]. American Association for the Study of Liver Diseases (AASLD) in 2018 defined HBV reactivation as:HBsAg positive and anti-HBC positive patients who meet one of the following criteria can be considered as HBV reactivation. (i) Compared with baseline, HBV DNA level ≥ 2log (100-fold) increased; (ii) For patients with low to undetectable baseline HBV DNA, the HBV DNA level increased by ≥ 3log (1000) IU/ml; (iii) For those with baseline HBV DNA deficiency, HBV DNA ≥ 4log (10,000) IU/ml. As for HBsAg negative and anti-HBC positive patients, HBV reactivation is considered when the following conditions are met: detectable HBV DNA or reverse serologic conversion of HBsAg (negative to positive). HBV reactivation-associated hepatitis exacerbation is defined as an ALT elevation ≥ 3 times the baseline level and an absolute value > 100 U/L [58].

The risk of HBV reactivation is 5–8 times higher in HBsAg-positive patients than in HBsAg-negative patients. The high-frequency of HBsAg positivity rate in lymphoma patients determines the high stake of HBV reactivation. Studies have shown that 38-73% of patients with HBsAg-positive NHL developed to HBV reactivation condition after chemotherapy [59]. Mild HBV reactivation may be characterized by asymptomatic ALT elevation and spontaneous remission in some patients.

Whereas severe reactivation may present with signs of liver failure such as jaundice, ascites, coagulation abnormalities and hepatic encephalopathy, which is characterized by rapid onset, uncontrollable, extremely high mortality and terrible prognosis. HBV reactivation increases the morbidity and mortality associated with hepatitis, leading to interruption of effective lymphoma treatment measures, and therefore requires special attention in clinical practice for patients with HBV-related DLBCL. HBV reactivation increases hepatitis relevant morbidity and mortality in DLBCL patients and leads to interruption of effective lymphoma treatment measures. Therefore, great attention should be paid to patients with HBV-associated DLBCL in clinical practice.

1.3.2 Mechanism of HBV reactivation

The risk of HBV reactivation in lymphoma patients depends on a variety of factors, including virological factors, influence of tumor treatment regimen, host factors and so on. Researchers found that high viral load at baseline was the most important risk factor for HBV reactivation, and HBV DNA level > 2000IU/ml was an independent risk factor for hepatitis caused by HBV reactivation (OR = 4.22, $P = 0.0046$) [60]. HBSAg positive patients had a higher reactivation rate than HBsAg negative /HBcAb positive patients [61]. The incidence of reactivation in HBsAg-positive patients was approximately 24-53%. In contrast, the reactivation rate of HBsAg negative, anti-HBC positive and/or anti-HBs positive patients after chemotherapy was only 1-2.7%. Because of the existence of cccDNA, HBV remains hardly to be completely eliminated even after achieving a clinical functional cure. Immunochemotherapy in lymphoma patients may affect the host immune response to the virus inducing HBV activation Steroids and anthracyclines are known risk factors for HBV reactivation. Steroids can directly stimulate viral replication and increase HBsAg content through glucocorticoid response elements in the HBV genome, affect T cell activity, block the cytotoxicity of HBV-specific cytotoxic T lymphocytes, thereby increasing the probability of HBV reactivation [59, 62]. Anthracyclines inhibit lymphocyte function, reduce tumor necrosis factor production, and enhance viral replication [63]. Breakthroughs in the treatment of lymphoma have been achieved with the widespread application of the targeted drug rituximab (RTX). Unfortunately, rituximab increased the risk of HBV reactivation by more than 5-fold, mainly due to depletion of B cells by RTX, which interferes with HBsAb production and its neutralizing effect on HBsAg. RTX attenuates HBV infection-related B cell antigen presentation and suppresses CD4 + T lymphocyte immune activity [64–66]. In addition, HBV reactivation and serologic conversion are more common in groups receiving hematopoietic stem cell transplantation and may be associated with pre-transplant immune clearance and post-transplant immunosuppressive therapy [67]. CD19-CAR-T is a promising new approach for the treatment of refractory relapsed B-cell lymphoma, which may be a curative therapy. *Yang* [68] et al. showed a high incidence of HBV reactivation (20%) with CD19-CAR-T cell therapy and HBeAg positivity might be a high risk factor for viral reactivation. Regrettably, the study was deficient in terms of small sample size for this reason the relationship between CAR-T and HBV reactivation needs to be confirmed by further in-depth verification. Moreover, the influence of host factors on HBV reactivation should not be ignored. Host factors include gender, age, having cirrhosis and underlying disease requiring

transplantation, with gender as male being the factor most strongly associated with increased risk of HBV reactivation [69]. DLBCL itself make inroads on lymphatic system and interferes with the body's immunity leading to HBV reactivation. In conclusion, the risk of HBV reactivation should be fully considered in the decision-making of HBC-associated DLBCL, regular serological and virological monitoring should be performed and necessary measures should be taken to prevent the occurrence of HBV reactivation.

1.3.3 Therapeutic strategies to prevent HBV reactivation

Principle and timing HBV-associated DLBCL receiving moderate or higher doses of glucocorticoids for more than 4 weeks or using B-cell monoclonal antibodies, anthracycline derivatives are high risk factors for HBV reactivation (>10%) [69].*Wu* [70] et al. identified HBV-associated DLBCL with >8 cycles of RTX based chemotherapy regimen plus low LMR(lymphocyte/monocyte ratio) at initial diagnosis as an "ultra-high risk" for HBV reactivation. Therefore, patients with DLBCL should be routinely screened for serologic markers including HBsAg, HBcAb and HBV DNA viral load before treatment to identify high-risk population early and prevention should be carried out before reactivation. Aiming to avoid HBV reactivity in an immunosuppressive state to the greatest extent, so as to reduce hepatocyte injury and ensure ideal liver function. Phase III GOYA and GALLIUM studies proved that prophylactic nucleos(t)ide analog therapy (NAT) in high-risk $HBsAg^{-}HBcAb^{+}$ B-NHL patients receiving anti-CD20 gents obinutuzumab or rituximab in first line was effective in preventing HBV reactivation [71]. A retrospective analysis in Japan showed that in DLBCL patients receiving the R-CHOP regimen, although HBsAg status had no significant effect on OS, among HBsAg-positive patients, 4-year OS was better in the group receiving lamivudine (LMV) (84.7%, 95% CI: 59.7-94.8%) and entecavir (ETV) (78.0%, 95% CI: 67.3-85.5%) prophylaxis than in the no nucleos(t)ide analogue (non–NA) group (55.6%, 95% CI: 20.4-80.5%) ($P=0.049$). Prophylactic use of ETV (3.8%) reduced the 4-year incidence of HBV reactivation-associated hepatitis compared with the LMV group (15.0%) and no prophylaxis group (33.3%). 4y cumulative mortality was significantly lower in the ETV group (non-NA: 33.3%, LAM: 5.0%, ETV: 0%), even in patients with high HBV-DNA load [72]. Nevertheless, in view of the side effects and drug resistance of NAT, prophylactic treatment is not recommended for all patients. It is important for HBV-associated DLBCL to grasp accurate NAT time. The Asia Pacific Association for the Study of the Liver recommends antiviral therapy for HBsAg-positive patients prior to immunosuppressive therapy or chemotherapy. Patients who are HBsAg-negative and anti-HBc-positive can be monitored closely if they have good monitoring compliance. When long-term or high-dose immunosuppressive or cytotoxic drugs (especially monoclonal antibodies against B or T lymphocytes) are given, antiviral therapy should be added promptly if there is a positive shift. In addition, antiviral therapy may be administered first in cases when the risk of using new chemotherapeutic and immunotherapeutic agents cannot be predicted [73]. The European Society of Hepatology recommended that all HBsAg positive patients receiving immunosuppression or chemotherapy should receive antinucleoside drugs as treatment or prophylaxis; HBsAg-negative, anti-HBc-positive individuals should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation [74].

Drug selection Currently, there are two major classes of drugs used for the antiviral treatment of chronic hepatitis B: alpha-interferon and nucleoside (acid) analogues. Alpha-interferon has a low viral response rate and is associated with significant myelosuppressive adverse effects, and is therefore not suitable for antiviral treatment of lymphoma patients. Nucleoside (acid) analogs competitively bind viral reverse transcriptase or RNA polymerase and thereby inhibit viral replication. These drugs include lamivudine (LMV), adefovir (TDF), telbivudine, entecavir (ETV), and tenofovir (TAF) [75]. Lamivudine was the most commonly used drug to prevent HBV reactivation in early studies, whose safety and efficacy have been confirmed. *Loomba* [76]et al. concluded that prophylactic treatment with lamivudine reduced the risk of HBV reactivation in HBsAg-positive patients on chemotherapy. NHL patients receiving CHOP regimen chemotherapy were less likely to experience HBV reactivation (11.5% vs. 56%, $P=0.001$), HBV-related hepatitis (7.7% vs. 48%, $P=0.001$), or severe hepatitis (0 vs. 36%, $P<0.001$) with prophylactic but not therapeutic application of LVM [77]. *Loglio's* [78] study included 85 HBsAg-negative/anti-HBc-positive NHL patients receiving RTX-based immunochemotherapy prophylactically treated with LVM was effective in preventing HBV reactivation, with a 50% decrease in anti-HBs titers in 35% of patients, twelve of whom were seronegative for anti-HBs. However, the drug resistance rate of LVM is high, and in recent years highly effective, low resistance antiviral drugs entecavir and tenofovir disoprox have received increasing attention. A retrospective analysis found that entecavir was more effective than lamivudine in preventing HBV reactivation in lymphoma patients treated with chemotherapy (0 vs. 12.4%, $P=0.024$). Entecavir is recommended as a primary prophylactic agent in III-IV

stage NHL. *Lin* [79]et al. recruited 121 HBsAg-positive DLBCL patients were treated with antiviral drugs from 1 week before R-CHOP to 6 months after chemotherapy. The incidence of HBV-related hepatitis in entecavir group was 13.3% lower than that in lamivudine group (0% vs. 13.3%, $P=0.003$). The HBV reactivation rate was decreased by 23.4% (6.6% vs. 30%, $P=0.001$), and the chemotherapy interruption rate was decreased by 16.7% (1.6% vs. 18.3%, $P=0.002$). Tenofovir prophylactic antiviral strategy is effective in controlling HBV reactivation during immunosuppressive therapy [80]. A prospective study evaluated the efficacy and safety of R-CHOP chemotherapy with TDF or LVM for prevention of HBV reactivation in patients with serum HBsAg-positive advanced DLBCL. The results showed that 15 of 38 patients in LAM cohort had urgent HBV DNA or aggravate HBV replication but none of 39 patients in the TDF cohort (95% CI: 0.229–0.553; $P<0.0001$). The incidence of HBV-related acute hepatitis ($P=0.054$) and early HBV reactivation ($P=0.012$) were lower in the TDF cohort than in LAM cohort. The incidence of adverse effects, including nephrotoxicity and osteoporosis, was similar in both cohorts [81]. It is important to optimize antiviral strategy for HBV-associated DLBCL. The guidelines recommend that for patients with baseline HBV DNA $\geq$ 2000 IU/ml and/or an expected duration of therapy > 12 months, highly potent and low-resistance antiviral drugs such as entecavir and tenofovir are preferred when available. For patients with baseline HBV DNA < 2000 IU/ml and expected duration of treatment $\leq$ 12 months, nucleoside antivirals such as lamivudine, telbivudine, entecavir and tenofovir can be selected [82].

Monitoring and discontinuation time During the treatment of HBV-associated DLBCL, hepatitis B serum immunological markers, liver function, and HBV DNA quantification are continuously monitored. Close follow-up is also required after the end of treatment. After the completion of treatment, the above indicators should be monitored once every 3 months for at least 12 months.

There is still no conclusion on the timing of discontinuing of HBV-associated DLBCL. Currently, it is suggested that patients with baseline HBV DNA $\geq$ 2000 IU/ml should consult with hepatologists or infectious disease physicians to decide the time of withdrawal. For patients with baseline HBV DNA < 2000 IU/ml, antiviral therapy should be continued for at least 6 to 12 months after completion of chemotherapy or immunosuppressive therapy. For high-risk groups, such as those receiving immunochemotherapy, hematopoietic stem cell transplantation or patients with cirrhosis, antiviral therapy should be continued for at least 12 months. For patients receiving rituximab maintenance therapy, antiviral therapy should be maintained [58, 73, 83, 84].

2 Conclusion and perspectives

Continuous exploration and research on the epidemiology of HBV-associated DLBCL, the pathogenesis of HBV-driven NHL, and biological heterogeneity have been conducive to a deeper understanding of HBV-associated DLBCL, which is crucial for guiding treatment decisions. The advent of DLBCL treatment provides more alternative options for disease control, but the consequent HBV reactivation problem cannot be ignored. For patients with HBV-associated DLBCL, the control of HBV infection and the prevention of HBV reactivation rely on the full cooperation between oncologists and infectious physicians. Timely identification of high-risk groups, HBV surveillance and prevention based on antiviral drugs are required while safeguarding the efficacy of DLBCL treatment and providing more clinical benefits to patients.

Abbreviations

DLBCL	Diffuse large B cell lymphoma
HBV	Hepatitis B virus
NHL	Non-Hodgkin lymphoma
CHB	Chronic HBV infection
cccDNA	covalently closed circular DNA
HBcAb	Hepatitis B core antibody
HCC	Hepatocellular carcinoma
ABC	Activated B cell-like
GCB	Germinal center B-cell
ASCT	Autologous hematopoietic stem cell transplantation
OBI	Occult hepatitis B infection
CI	Confidence intervals
OR	Odds ratio
HCV	Hepatitis C virus
BCR	B cell receptor
SHM	Somatic hypermutation
AtMBCs	Atypical memory B cells
AID	Activation-induced cytosine deaminase
TIME	Tumor immune microenvironment
Treg	Regulatory T cells
APOBEC	Apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like
MHC-II	Major histocompatibility complex II
DC	Dendritic cells
IPI	International prognostic index
PFS	Progression free survival
OS	Overall survival
AASLD	American Association for the Study of Liver Diseases
RTX	Rituximab
NAT	Nucleos(t)ide analog therapy
LMV	Lamivudine
TDF	Adefovir
ETV	Entecavir
TAF	Tenofovir

Acknowledgements
We thank all authors for their contributions to this manuscript.

Authors' contributions
ZJY designed and drafted the manuscript, ZQY reviewed and modified this manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors approved the final manuscript.

Competing interests
All authors declare that they have no conflict of interest.

Received: 4 May 2023 Accepted: 9 October 2023
Published online: 20 October 2023

References

1. Sehn LH, Salles G. Diffuse large B-cell Lymphoma. N Engl J Med. 2021;384(9):842–58.
2. Sheena BS, Hiebert L, Han H, et al. Global, regional, and national burden of Hepatitis B, 1990–2019: a systematic analysis for the global burden of Disease Study 2019. The Lancet Gastroenterology Hepatol. 2022;7:796–829. 9.
3. McNaughton AL, D'Arienzo V, Ansari MA, et al. Insights from deep sequencing of the HBV genome—unique, tiny, and misunderstood. Gastroenterology. 2019;156(2):384–99.
4. Ko C, Chakraborty A, Chou WM, et al. Hepatitis B virus genome recycling and de novo secondary Infection events maintain stable cccDNA levels. J Hepatol. 2018;69(6):1231–41.
5. Yuen MF, Chen DS, Dusheiko GM, et al. Hepatitis B virus Infection. Nat Reviews Disease Primers. 2018;4(1):1–20.
6. Nassal M. HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic Hepatitis B. Gut. 2015;64(12):1972–84.
7. Mouzannar K, Liang TJ. Hepatitis B virus–recent therapeutic advances and challenges to cure. J Hepatol. 2020;73(3):694–5.
8. Razavi-Shearer D, Gamkrelidze I, Nguyen MH, et al. Global prevalence, treatment, and prevention of Hepatitis B virus Infection in 2016: a modelling study. The lancet Gastroenterology and hepatology. 2018;3:383–403. 6.
9. Wang H, Men P, Xiao Y, et al. Hepatitis B Infection in the general population of China: a systematic review and meta-analysis. BMC Infect Dis. 2019;19(1):1–10.
10. Siegel R, Miller K, Fuchs H, et al. Cancer Stat 2022. CA Cancer J Clin. 2022;72(1):7–33.
11. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell Lymphoma identified by gene expression profiling. Nature. 2000;403(6769):503–11.
12. Poletto S, Novo M, Paruzzo L, et al. Treatment strategies for patients with diffuse large B-cell Lymphoma. Cancer Treat Rev. 2022;10:102443.
13. Ernst M, Oeser A, Besiroglu B, et al. Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell Lymphoma. Cochrane Database Syst Rev. 2021;9(9):CD013365.
14. Wilson WH, Wright GW, Hodkinson B, et al. Effect of ibrutinib with R-CHOP chemotherapy in genetic subtypes of DLBCL. Cancer Cell. 2021;39(12):1643–53.
15. Nowakowski GS, Chiappella A, Gascoyne RD, et al. ROBUST: a phase III study of lenalidomide plus R-CHOP versus placebo plus R-CHOP in previously untreated patients with ABC-type diffuse large B-cell Lymphoma. J Clin Oncol. 2021;39(12):1317.
16. Cassim S, Antel K, Chetty DR, et al. Diffuse large B-cell Lymphoma in a South African cohort with a high HIV prevalence: an analysis by cell-of-origin, Epstein–Barr virus Infection and survival. Pathology. 2020;52(4):453–9.
17. Galun E, Livni N, Ketzinel M, et al. Hepatitis B virus Infection associated with hematopoietic tumors. Am J Pathol. 1994;145(5):1001.
18. Li M, Gan Y, Fan C, et al. Hepatitis B virus and risk of non-hodgkin Lymphoma: an updated meta-analysis of 58 studies. J Viral Hepatitis. 2018;25(8):894–903.
19. Ulcickas Yood M, Quesenberry CP Jr, Guo D, et al. Incidence of Non-hodgkin's Lymphoma among individuals with chronic Hepatitis B virus Infection. Hepatology. 2007;46(1):107–12.
20. Su TH, Liu CJ, Tseng TC, et al. Chronic hepatitis B is associated with an increased risk of B-cell non-Hodgkin's lymphoma and multiple myeloma. Aliment Pharmacol Ther. 2019;49:589–98. 5.
21. Engels EA, Cho ER, Jee SH. Hepatitis B virus Infection and risk of non-hodgkin Lymphoma in South Korea: a cohort study. Lancet Oncol. 2010;11(9):827–34.
22. Mahale P, Engels EA, Koshiol J. Hepatitis B virus Infection and the risk of cancer in the elderly US population. Int J Cancer. 2019;144(3):431–9.
23. Chen MH, Hsiao LT, Chiou TJ, et al. High prevalence of occult Hepatitis B virus Infection in patients with B cell non-hodgkin's Lymphoma. Ann Hematol. 2008;87(6):475–80.
24. Nath A, Agarwal R, Malhotra P, et al. Prevalence of Hepatitis B virus Infection in non-hodgkin Lymphoma: a systematic review and meta-analysis. Intern Med J. 2010;40(9):633–41.
25. Wang F, Xu R, Han B, et al. High incidence of Hepatitis B virus Infection in B-cell subtype non-Hodgkin Lymphoma compared with other cancers. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2007;109(7):1360–4.
26. Quinn ER, Chan CH, Hadlock KG, et al. The B-cell receptor of a Hepatitis C virus (HCV)–associated non-hodgkin Lymphoma binds the viral E2 envelope protein, implicating HCV in lymphomagenesis. Blood J Am Soc Hematol. 2001;98(13):3745–9.
27. Tucci FA, Kitanovski S, Johansson P, et al. Biased IGH VDJ gene repertoire and clonal expansions in B cells of chronically Hepatitis C virus–infected individuals. Blood. J Am Soc Hematol. 2018;131(5):546–57.
28. Deng L, Song Y, Young KH, et al. Hepatitis B virus-associated diffuse large B-cell Lymphoma: unique clinical features, poor outcome, and Hepatitis B surface antigen-driven origin. Oncotarget. 2015;6(28):25061.
29. Huang CE, Yang YH, Chen YY, et al. The impact of Hepatitis B virus Infection and vaccination on the development of non-hodgkin Lymphoma. J Viral Hepatitis. 2017;24(10):885–94.
30. Venturutti L, Melnick AM. The dangers of déjà vu: memory B cells as the cells of origin of ABC-DLBCLs. Blood. 2020;136(20):2263–74.
31. Sutton HJ, Aye R, Idris AH, et al. Atypical B cells are part of an alternative lineage of B cells that participates in responses to vaccination and Infection in humans. Cell Rep. 2021;34(6): 108684.
32. Bal E, Kumar R, Hadigol M, et al. Super-enhancer hypermutation alters oncogene expression in B cell Lymphoma. Nature. 2022;607(7920):808–15.
33. Lim CJ, Lee YH, Pan L, et al. Multidimensional analyses reveal distinct immune microenvironment in Hepatitis B virus-related hepatocellular carcinoma. Gut. 2019;68(5):916–27.
34. Burton AR, Pallett LJ, McCoy LE, et al. Circulating and intrahepatic antiviral B cells are defective in Hepatitis B. J Clin Investig. 2018;128(10):4588–603.
35. Salimzadeh L, Le Bert N, Dutertre CA, et al. PD-1 blockade partially recovers dysfunctional virus–specific B cells in chronic Hepatitis B Infection. J Clin Investig. 2018;128(10):4573–87.
36. Ren W, Ye X, Su H, et al. Genetic landscape of Hepatitis B virus-associated diffuse large B-cell Lymphoma. Hematol Oncol. 2018;35(24):279–279.
37. Ye X, Ren W, Liu D, et al. Genome-wide mutational signatures revealed distinct developmental paths for human B cell Lymphomas. J Exp Med. 2021;218(2):e20200573.
38. Chapuy B, Stewart C, Dunford AJ, et al. Molecular subtypes of diffuse large B cell Lymphoma are associated with distinct pathogenic mechanisms and outcomes. Nat Med. 2018;24(5):679–90.
39. Pecori R, Di Giorgio S, Paulo Lorenzo J, et al. Functions and consequences of AID/APOBEC-mediated DNA and RNA deamination. Nat Rev Genet. 2022;23(8):1–14.
40. Mertz TM, Collins CD, Dennis M, et al. APOBEC-Induced Mutagenesis in Cancer. Annu Rev Genet. 2022;56:229–52.

41. Petljak M, Dananberg A, Chu K, et al. Mechanisms of APOBEC3 mutagenesis in human cancer cells. Nature. 2022;607(7920):799–807.
42. Zhang X, Wu Z, Hao Y, et al. Aberrantly activated APOBEC3B is associated with mutant p53-driven refractory/relapsed diffuse large B-cell lymphoma. Front Immunol. 2022;13:888250. https://doi.org/10.3389/fimmu.2022.888250.
43. Dominguez-Sola D, Kung J, Holmes AB, et al. The FOXO1 transcription factor instructs the germinal center dark zone program. Immunity. 2015;43(6):1064–74.
44. Li M, Shen Y, Chen Y, et al. Characterization of Hepatitis B virus Infection and viral DNA integration in non-hodgkin Lymphoma. Int J Cancer. 2020;147(8):2199–209.
45. Yin J, Li N, Han Y, et al. Effect of antiviral treatment with nucleotide/nucleoside analogs on postoperative prognosis of Hepatitis B virus-related hepatocellular carcinoma: a two-stage longitudinal clinical study. J Clin Oncol. 2013;31(29):3647–55.
46. Benedict Yen T, Hepadnaviral X. Protein: review of recent progress. J Biomed Sci. 1996;3(1):20–30.
47. Huang X, Young KH, Guo W, et al. Identification of Hepatitis B virus aetiologic antigens, HBx and Pre-S2, in diffuse large B-cell Lymphoma. J Viral Hepatitis. 2020;27(9):948–50.
48. Li J, Chen Y, Guo X, et al. lncNBAT1/APOBEC3A is a mediator of HBX-induced chemoresistance in diffuse large B cell Lymphoma cells. Mol Therapy-Nucleic Acids. 2022;27:1064–77.
49. Ye X, Wang L, Nie M, et al. A single-cell atlas of diffuse large B cell Lymphoma. Cell Rep. 2022;39(3): 110713.
50. Buschow SI, Biesta PJ, Groothuismink ZM, et al. TLR7 polymorphism, sex and chronic HBV Infection influence plasmacytoid DC maturation by TLR7 ligands. Antiviral Res. 2018;157:27–37.
51. Arima S, Akbar S, Michitaka K, et al. Impaired function of antigen-presenting dendritic cells in patients with chronic Hepatitis B: localization of HBV DNA and HBV RNA in blood DC by in situ hybridization. Int J Mol Med. 2003;11(2):169–74.
52. Fang Y, Wang L, Qian Y, et al. Efficacy and prognostic analysis of relapsed/refractory diffuse large B-cell Lymphoma patients with Hepatitis B virus Infection. Xueyexue Zazhi. 2018;39(12):1017–20.
53. Wang Y, Wang H, Pan S, et al. Capable Infection of Hepatitis B virus in diffuse large B-cell Lymphoma. J Cancer. 2018;9(9):1575.
54. Liu Z, Li S, Guo W, et al. MYC gene rearrangements are closely associated with poor survival of diffuse large B cell lymphoma with hepatitis B virus infection. BioMed Res Int. 2017;2017:1967648.
55. Law M, Lai H, Chan H, et al. The impact of Hepatitis B virus (HBV) Infection on clinical outcomes of patients with diffuse large B-cell Lymphoma. Eur J Cancer Care. 2015;24(1):117–24.
56. Liu WP, Wang XP, Zheng W, Ping LY, et al. Hepatitis B virus reactivation after withdrawal of prophylactic antiviral therapy in patients with diffuse large B cell Lymphoma. Leuk Lymphoma. 2016;57(6):1355–62.
57. Keam B, Lee JH, Im SA, et al. Why, when, and how to prevent Hepatitis B virus reactivation in cancer patients undergoing chemotherapy. J Natl Compr Canc Netw. 2011;9(5):465–77.
58. Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic Hepatitis B: AASLD 2018 Hepatitis B guidance. Hepatology. 2018;67(4):1560–99.
59. Cheng AL, Hsiung CA, Su IJ, et al. Steroid-free chemotherapy decreases risk of Hepatitis B virus (HBV) reactivation in HBV-carriers with Lymphoma. Hepatology. 2003;37(6):1320–8.
60. Jang JW, Choi JY, Bae SH, et al. A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. Hepatology. 2006;43(2):233–40.
61. Loras C, Gisbert JP, Mínguez M, et al. Liver dysfunction related to Hepatitis B and C in patients with inflammatory bowel Disease treated with immunosuppressive therapy. Gut. 2010;59(10):1340–6.
62. Chou CK, Wang LH, Lin HM, et al. Glucocorticoid stimulates Hepatitis B viral gene expression in cultured human hepatoma cells. Hepatology. 1992;16(1):13–8.
63. Voican C, Mir O, Loulergue P, et al. Hepatitis B virus reactivation in patients with solid tumors receiving systemic anticancer treatment. Ann Oncol. 2016;27(12):2172–83.
64. Xu X, Shang Q, Chen X, et al. Reversal of B-cell hyperactivation and functional impairment is associated with HBsAg seroconversion in chronic Hepatitis B patients. Cell Mol Immunol. 2015;12(3):309–16.
65. Kim SJ, Hsu C, Song YQ, et al. Hepatitis B virus reactivation in B-cell Lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. Eur J Cancer. 2013;49(16):3486–96.
66. Elbedewy TA, Elashtokhy HEA, Rabee ES, et al. Prevalence and chemotherapy-induced reactivation of occult Hepatitis B virus among Hepatitis B surface antigen negative patients with diffuse large B-cell Lymphoma: significance of Hepatitis B core antibodies screening. J Egypt Natl Cancer Inst. 2015;27(1):11–8.
67. Gentile G, Andreoni M, Antonelli G, et al. Screening, monitoring, prevention, prophylaxis and therapy for Hepatitis B virus reactivation in patients with haematologic malignancies and patients who underwent haematologic stem cell transplantation: a systematic review. Clin Microbiol Infect. 2017;23(12):916–23.
68. Yang C, Xie M, Zhang K, et al. Risk of HBV reactivation post CD19-CAR-T cell therapy in DLBCL patients with concomitant chronic HBV Infection. Leukemia. 2020;34(11):3055–9.
69. Chen Z, Diaz G, Pollicino T, et al. Role of humoral immunity against hepatitis B virus core antigen in the pathogenesis of acute liver failure. Proc Nat Acad Sci. 2018;115(48):E11369–78.
70. Wu CY, Hsiao LT, Chiou TJ, et al. Lymphocyte/monocyte ratio and cycles of rituximab-containing therapy are risk factors for Hepatitis B virus reactivation in patients with diffuse large B-cell Lymphoma and resolved Hepatitis B. Leuk Lymphoma. 2015;56(8):2357–64.
71. Kusumoto S, Arcaini L, Hong X, et al. Risk of HBV reactivation in patients with B-cell Lymphomas receiving obinutuzumab or rituximab immunochemotherapy. Blood J Am Soc Hematol. 2019;133(2):137–46.
72. Yamauchi N, Maruyama D, Choi I, et al. Prophylactic antiviral therapy for Hepatitis B virus surface antigen-positive patients with diffuse large B-cell Lymphoma treated with rituximab-containing chemotherapy. Cancer Sci. 2021;112(5):1943–54.
73. Lau G, Yu ML, Wong G, et al. APASL clinical practice guideline on Hepatitis B reactivation related to the use of immunosuppressive therapy. Hep Intl. 2021;15(5):1031–48.
74. Liver EAFTSOT. EASL 2017 clinical practice guidelines on the management of Hepatitis B virus Infection. J Hepatol. 2017;67(2):370–98.
75. Fanning GC, Zoulim F, Hou J, et al. Therapeutic strategies for Hepatitis B virus Infection: towards a cure. Nat Rev Drug Discovery. 2019;18(11):827–44.
76. Loomba R, Rowley A, Wesley R, et al. Systematic review: the effect of preventive lamivudine on Hepatitis B reactivation during chemotherapy. Ann Intern Med. 2008;148(7):519–28.
77. Hsu C, Hsiung CA, Su IJ, et al. A revisit of prophylactic lamivudine for chemotherapy-associated Hepatitis B reactivation in non-Hodgkin's Lymphoma: a randomized trial. Hepatology. 2008;47(3):844–53.
78. Loglio A, Viganò M, Grossi G, et al. Lamivudine prophylaxis prevents Hepatitis B virus reactivation in anti-HBc positive patients under Rituximab for non-hodgkin Lymphoma. Dig Liver Disease. 2019;51(3):419–24.
79. Huang H, Li X, Zhu J, et al. Entecavir vs lamivudine for prevention of Hepatitis B virus reactivation among patients with untreated diffuse large B-cell Lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. JAMA. 2014;312(23):2521–30.
80. Koskinas J, Deutsch M, Adamidi S, et al. The role of tenofovir in preventing and treating Hepatitis B virus (HBV) reactivation in immunosuppressed patients. A real life experience from a tertiary center. Eur J Intern Med. 2014;25(8):768–71.
81. Picardi M, Della Pepa R, Giordano C, et al. Tenofovir versus Lamivudine for the prevention of Hepatitis B virus reactivation in advanced-stage DLBCL. Blood. 2019;133(5):498–501.
82. Hu J, Protzer U, Siddiqui A. Revisiting Hepatitis B virus: challenges of curative therapies. J Virol. 2019;93(20):e01032–01019.
83. Kusumoto S, Tanaka Y, Suzuki R, et al. Monitoring of Hepatitis B virus (HBV) DNA and risk of HBV reactivation in B-cell Lymphoma: a prospective observational study. Clin Infect Dis. 2015;61(5):719–29.
84. Mori S, Fujiyama S. Hepatitis B virus reactivation associated with antirheumatic therapy: risk and prophylaxis recommendations. World J Gastroenterology: WJG. 2015;21(36): 10274.

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