Hepatitis B reactivation

Subjects: Virology

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Hepatitis B reactivation is a common complication in lymphoma patients under immunosuppressive treatment with potentially serious and life-threating consequences.

hepatitis B reactivation | lymphoma | immunosuppressive therapy | nucleoside analogues

1. Introduction

Hepatitis B virus (HBV) is an enveloped DNA virus that can cause a potentially life- threatening liver disease, such as liver failure and/or hepatocellular carcinoma. Although HBV vaccination and effective drugs for suppression of HBV have been widely applied in world, HBV infection is still a global health problem. Hepatitis B reactivation mostly occurs in the context of an immunosuppressed status and has been commonly reported in cancer patients receiving chemotherapy or target therapy. HBV reactivation will cause significant morbidity and mortality if not appropriately diagnosed and managed. Clinicians should be aware of HBV reactivation and screen for HBV before implementing an immunosuppressive regimen and keep monitoring HBV status in high-risk population.

HBV reactivation has been an identified risk in lymphoma patients treated with cytotoxic chemotherapies (e.g., anthracyclines), high-dose corticosteroids, and anti-CD20 monoclonal antibody, rituximab. More and more novel agents, such as anti-CD30 monoclonal antibody, anti-CD52 monoclonal antibody, and small molecular inhibitors targeting Bruton tyrosine kinase (BTK), B-cell lymphoma-2 (BCL-2), phosphoinositide 3-kinase (PI3K), and even chimeric antigen receptor (CAR) T-cell immunotherapy have been used to treat malignant lymphoma in recent years. However, the risk of HBV reactivation in these novel agents is still undetermined.

HBV reactivation indicates the recurrence of active inflammatory disease in patients in the inactive phase of chronic hepatitis B (CHB) or those recovered from past infection. The definition of HBV reactivation varies between different guidelines, but the general principle is similar. In patients with CHB, HBsAg-positive at least 6 months, the reactivation is defined by an increase in HBV DNA level compared to baseline. In patients with resolved HBV infection, HBsAg-negative and anti-HBc-positive, reactivation is defined by the detection of HBV DNA or reappearance of HBsAg. Table 2 is the summary of definitions of HBV reactivation based on different society guidelines. A hepatitis flare is defined as ≥3-fold increase in ALT level compared to baseline and >100 U/L [1].

Table 2. Definitions of HBV reactivation based on different society guidelines.

Society	Reactivaion of CHB	Reactivation of Resolved HBV
American Association for the Study of Liver Diseases (AASLD) 2018 guideline [1]	Any of the following: • Unavailable DNA baseline: ≥10,000 IU/mL • Available DNA baseline, previously undetectable: ≥1000 IU/mL • Available DNA baseline, previously detectable: ≥100-fold increase	Any of the following: • Development of detectable DNA • Reappearance of HBsAg (also known as reverse seroconversion)
American Gastroenterological Association (AGA) 2015 guideline [2]	• Unavailable DNA baseline: not explicitly defined • Available DNA baseline, previously undetectable: de novo detectable DNA • Available DNA baseline, previously detectable: ≥10-fold increase	• Reverse seroconversion to HBsAg-positive status
The Asian Pacific Association for the Study of the Liver (APASL) 2016 guideline [3]	• Unavailable DNA baseline: ≥20,000 IU/mL • Available DNA baseline, previously undetectable: de novo detectable HBV DNA to a level of 100 IU/mL • Available DNA baseline, previously detectable: ≥2 log increase from baseline levels	• Not clearly defined
European Association for the Study of the Liver (EASL) 2017 guideline [4]	• No clearly defined	• Not clearly defined
Korean Association for the Study of the Liver (KASL) 2019 guideline [5]	• An increase in serum HBV DNA by more than 100 times the baseline level	• Seroconversion of HBsAg-negative to positive

Society	Reactivaion of CHB	Reactivation of Resolved HBV
		• Detection of serum HBV DNA from none to positive
American Society of Clinical Oncology (ASCO) 2020 update [6]	• The same as the AASLD guidelines	• The same as the AASLD guidelines

2. Risk Factors for HBV Reactivation

2.1. Host Factors

In previous studies, older age and male sex have been identified as risk factors for HBV reactivation [7][8][9][10]. In addition, a survey of 1692 patients with hematologic malignancy found that diabetes mellitus, liver cirrhosis, and hepatocellular carcinoma were independent risk factors of HBV reactivation [11]. All these findings indicate that the immunocompromised host is a significant risk factor for HBV reactivation.

2.2. Virological Factors

HBV infection causes covalently closed circular DNA (cccDNA) in hepatocytes, regardless of HBsAg or HBV DNA status. The cccDNA is quite stable in infected cells and can persist in a latent state. The persistence of cccDNA is the key driver for HBV reactivation [12]. HBsAg positivity, HBeAg positivity and the high HBV DNA levels before immunosuppressive therapy have also been known risk factors for HBV reactivation [13][14][15][16]. The risk of HBV reactivation is five- to eight-fold higher in HBsAg patients [16]. High HBV viral load prior to cytotoxic chemotherapy is a prominently predictive factor for HBV reactivation [15]. In resolved HBV infection patients, many studies showed that negative baseline anti-HBs carried a higher risk of HBV reactivation [9][10][17][18][19][20].

2.3. Immunosuppressive Regimens

2.3.1. Corticosteroids

Corticosteroids are used in the treatment of lymphoma for a long time. Firstly, corticosteroids upregulate the HBV glucocorticoid responsive element (a transcriptional regulatory element) and promote viral replications. Secondly, they cause a direct suppressive effect on cytotoxic T cells which is involved in HBV control [21]. The above two mechanisms explain the susceptibility to HBV reactivation in patients who receive corticosteroids. The immunosuppressive effect of steroids is dose and duration dependent.

2.3.2. Anti-CD20 Monoclonal Antibodies

Rituximab, an anti-CD20 monoclonal antibody widely used in lymphoma treatment, has been well known a vital risk factor for HBV reactivation. Several studies have reported the risk of HBV reactivation in rituximab treatment. Both HBsAg-positive and resolved HBV infection patients who receive these agents are susceptible to HBV reactivation [10][17][22][23][24][25][26][27].

2.3.3. Other Monoclonal Antibodies

Alemtuzumab, a monoclonal antibody against CD52, used to treat refractory CLL or as a conditioning regimen in hematopoietic stem cell transplantation, has been reported to induce HBV reactivation and related hepatitis. Two CLL subjects with occult HBV infection developing a virological and biochemical flare of hepatitis B following immunotherapy with alemtuzumab were reported [28]. Brentuximab vedotin, an antibody–drug conjugate medication, which targets tumor cells expressing CD30, is used for T cell lymphoma and relapsed or refractory Hodgkin lymphoma. A case of HBV reactivation was reported from China.

2.3.4. Other Novel Agents

Ibrutinib is used to treat mantle cell lymphoma, chronic lymphocytic leukemia, Waldenstrom macroglobulinemia, marginal zone lymphoma and chronic graft-versus-host disease in allo-hematopoietic stem cell transplantation. It inhibits (Bruton's tyrosine kinase (BTK) and thereby interrupts the B-cell receptor signaling pathway which regulates B cell proliferation and activation [29]. Idelalisib, a PI3K inhibitor, is approved for indolent lymphoma treatment. A total of 13–25% of patients reported grade 3 or higher elevations of serum aminotransferase levels and most cases are asymptomatic and resolved following dose reduction [30][31]. Bortezomib, a proteasome inhibitor, is used for treatment of multiple myeloma (MM) and mantle cell lymphoma, HBV reactivation occurred in six HBsAg-positive patients and two HBsAg -negative patients, including six who received autologous stem cell transplant (ASCT). Venetoclax is a potent inhibitor of the antiapoptotic BCL-2 protein and is used for CLL and acute myeloid leukemia treatment, it may have a potential risk of HBV reactivation.

2.3.5. Chimeric Antigen Receptor (CAR) T-Cell Immunotherapy

CAR T cell immunotherapy has recently been found to be a novel and effective treatment for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) [32][33][34][35].

3. Summary

HBV reactivation exerts a negative impact on the clinical outcomes in patients with malignant lymphoma. All patients should be screened for HBV status prior immunosuppressive therapy. The risk of HBV reactivation should be assessed by virological markers and immunosuppressive regimens individually. Given the efficacy of NAs against HBV, prophylactic therapy is a more effective strategy to manage HBV reactivation. Prophylaxis is recommended for all HBsAg-positive patients and HBsAg-negative, anti-HBc-positive patients with detectable HBV DNA or high risk for HBV reactivation. Liver function, HBsAg, and HBV DNA should continue to be monitored for at least 12 months after the cessation of prophylaxis. Several novel agents for lymphoma treatment have emerged in

recent years. However, only few HBV reactivation cases were reported. The real incidence and risk of HBV reactivation in these novel agents is still unclear to date. It is imperative to conduct larger studies to clarify the risk of HBV reactivation and provide a comprehensive guideline to prevent HBV reactivation during novel agent treatment.

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