Holistic Integrative Oncology

REVIEW

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Hepatitis B virus reactivation associated with CAR T-cell therapy

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Abstract

Patients with hematological malignancies who also have a hepatitis B virus (HBV) infection need to be aware of the potential risk of HBV reactivation when undergoing anti-cancer treatments. Among these treatments, CAR T-cell therapy has gained significant attention as a promising option, but it also raises concerns regarding HBV reactivation. This review aims to provide an overview of published reports on HBV reactivation during CAR T-cell therapy, along with an assessment of the effectiveness of prophylactic antiviral therapy. Additionally, we propose a systematic approach for monitoring and managing HBV reactivation during CAR T-cell therapy to enhance the safety of this treatment for patients with HBV infection.

Keywords Hepatitis B virus, Reactivation, CAR T-cell therapy, Hematological malignancies

1 Background

In recent times, a body of research has emerged indicating the potential occurrence of hepatitis B virus (HBV) reactivation during chimeric antigen receptor (CAR) T-cell therapy, which, fortunately, can be effectively mitigated through the administration of nucleotide analogs (NAs). It is noteworthy that China is situated within regions of high HBV endemicity, and individuals afflicted with HBV infection are at an increased risk of developing non-Hodgkin lymphoma (NHL) and diffuse large B-cell lymphoma (DLBCL).

Drawing upon insights from prior clinical investigations and expert consensus, our objective is to provide an actionable framework for healthcare professionals, enabling them to judiciously administer CAR T-cell therapy to patients grappling with hematological malignancies concurrent with HBV infection [1]. Our ultimate aim is to proactively address the potential challenge of HBV reactivation and its associated, potentially life-threatening complications. This endeavor is grounded in the latest advancements in research and clinical experience in this domain.

1.1 HBV infection and B-cell malignancies

Hepatitis B virus (HBV) is a global health concern, with a pervasive presence across the world. Approximately 257 million individuals are currently affected by HBV on a global scale, with a staggering 68% of these cases concentrated in the regions of Africa and the West Pacific [2]. In China, HBV presents a significant public health challenge, contributing to approximately one-third of the total global burden of HBV infections. Despite widespread vaccination efforts, the national prevalence of hepatitis B surface antigen (HBsAg) has declined to 5.2%. However, HBV continues to impact a substantial population, affecting roughly 70 million individuals annually, with 20–30 million cases evolving into chronic infections and tragically resulting in more than 880,000 deaths each year [3, 4]. Studies have shown that chronic HBV infection significantly increases the risk of NHL and DLBCL [5]. DLBCL patients with concomitant HBV infection have distinct clinical, genomic, and transcriptomic

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characteristics, indicating that HBV infection plays a contributory role in the development of B-cell malignancies [6]. In China, 9%-30.2% of NHL patients and approximately 25% of DLBCL patients harbor chronic HBV infections, and about 20%-44% of DLBCL patients have resolved HBV infections [7, 8]. Given the prevalence of HBV infection among patients with NHL or DLBCL, it is essential to recognize that the risk of HBV reactivation significantly escalates following exposure to immunosuppressive or cytotoxic agents [9].

The risk of HBV reactivation varies for each patient, depending on their HBV serological status as well as the specific anti-tumor treatment they receive. Because of the persistent B-cell aplasia induced by chemoimmunotherapy, the incidence of HBV reactivation ranges from 21 to 60% in patients with chronic HBV infection and varies from 2 to 25% in patients with resolved HBV infections [10, 11]. The risk of reactivation can be considered as high risk if the incidence of HBV reactivation reaches or exceeds 10%. Therefore, patients with either chronic or resolved HBV infection are at high risk of HBV reactivation when receiving hematopoietic stem cell transplantation or immunochemotherapy (including rituximab and glucocorticoid chemotherapy) [12, 13]. However, randomized controlled clinical studies have shown that the prophylactic use of NAs can reduce the risk of HBV reactivation in this patient cohort. Similarly, since CAR T cells targeting B cells or plasma cells can lead to long-lasting B-cell depletion and humoral immunodeficiency, patients with contaminant HBV infection might also face a high risk of HBV reactivation when undergoing CAR T-cell therapy.

1.2 HBV reactivation in the setting of CAR T-cell therapy

Recently, HBV reactivation has been described in patients with chronic HBV infection or resolved HBV infection after anti-CD19, CD20, CD22, or B-cell maturation antigen (BCMA) CAR T-cell therapy (Table 1). In a study including 19 patients with B-cell malignancies and concomitant chronic HBV infection, HBV reactivation and HBV-related severe hepatitis were detected in 1 (5.3%) patient at 4 months after anti-CD19 CAR T-cell infusion, although they had received entecavir (ETV) [14]. Similarly, in another 2 studies which included 15 and 12 patients with B-cell or plasma-cell malignancies and concomitant chronic HBV infection, respectively, 3 (20%) and 2 (16.7%) patients experienced HBV reactivation [15, 16]. Even with the continuous administration of NAs, HBV reactivation in these patients occurred mainly within 6 months after CAR T-cell infusion and manifested asymptomatically as an increase in HBV DNA copy number while without hepatitis flare. Because of the high incidence of HBV reactivation in these studies, patients with chronic HBV infection are at high risk of HBV reactivation when they receive CAR T-cell therapy targeting B cells or plasma cells.

While in the patients who had resolved HBV infection, no cases of HBV reactivation were reported during NAs administration, even in case of HBV DNA-positive. However, 2 independent studies each reported 1 patient (3.4–12.5%), who were HBV DNA-negative and did not receive prophylactic NAs, experienced asymptomatic HBV reactivation at 2 months and 6 months after CAR T-cell infusion, respectively [16, 21]. HBV reactivation in these 2 patients presented as an increase in HBV DNA copy number or a reverse seroconversion from HBsAg negativity to positivity and was promptly controlled by the preemptive use of NAs. These data demonstrate that patients with resolved HBV infection might be also at high risk of HBV reactivation after CAR T-cell infusion, and the administration of NAs can prevent HBV reactivation in these patients, regardless of the HBV DNA status.

Furthermore, HBV can be activated in these high-risk patients after improper withdrawal of prophylactic NAs. Four patients, involving 2 with chronic HBV infection and 2 with resolved HBV infection, experienced HBV reactivation after self-discontinuation of ETV [15, 17, 19, 26]. At the time of HBV reactivation, B-cell depletion or complete remission of disease was still sustained. One patient with chronic HBV infection self-discontinued the use of ETV only 1 month after CAR T-cell infusion, leading to a tragic outcome as the patient succumbed to fulminant hepatic failure just two months later [26]. This mournful incident underscores the critical importance prophylactic NAs are essential for high-risk patients. Similarly, another patient with resolved HBV infection ceased antiviral treatment five months after the CAR T-cell infusion, resulting in HBV reactivation just one month later. Despite prompt intervention with entecavir and tenofovir, the patient eventually succumbed to complications of hepatitis and cerebral hemorrhage [19]. The remaining two patients had been on ETV prophylaxis for more than 1 year before the discontinuation of ETV. They presented asymptomatic elevation of HBV DNA titer or hepatitis flare. After prompt recognition of these signs and the subsequent resumption of ETV treatments, HBV reactivation was successfully resolved in both patients [15, 17]. These outcomes provide compelling evidence that prophylactic NAs therapy may serve as a protective measure against HBV reactivation in patients undergoing CAR T-cell therapy, whether they have chronic HBV infection or resolved HBV infection.

It remains uncharted territory to fully understand the impact of CAR T-cell therapy on HBV reactivation in T-cell malignancies. A noteworthy case involves a patient

Table 1 Summary of HBV reactivation cases in CAR T-cell therapy

Study	Disease	Targets of CAR T-cell therapy	HBV characteristic at baseline	Numbers of reactivation/total	Prophylactic antiviral therapy	Clinical manifestations and outcomes
Strati P 2019 [17]	R/R-DLBCL	CD19	Resolved HBV infection	1/3	All received entecavir	Successfully treated with entecavir
Yang C 2020 [15]	R/R-DLBCL	CD19	Chronic HBV infection	3/15	All received entecavir or Lamivudine	Asymptomatic HBV reactivation
Lai P 2020 [18]	R/R B-ALL	CD19	Chronic HBV infection	0/3	All received entecavir or tenofovir	No HBV reactivation
Cui R 2020 [19]	7 R/R B-ALL and 13 R/R DLBCL	CD19	Chronic HBV infection	0/5	All received prophylactic entecavir or tenofovir	No HBV reactivation
Liu W 2020 [20]	R/R B-cell lymphoma	CD19	Chronic HBV infection	0/6	All 6 patients were on prophylactic entecavir	No HBV reactivation
			Resolved HBV infection	0/11	Only 2 of the 11 were on prophylactic entecavir or lamivudine	No HBV reactivation
Han L 2020 [21]	R/R MM	BCMA	Chronic HBV infection	0/1	All received entecavir or lamivudine	No HBV reactivation
			Resolved HBV infection	1/8	Only 2 of the 8 were on prophylactic entecavir or lamivudine	One asymptomatic HBV reactivation in no prophylactic group
Wang Y 2020 [16]	advanced B-cell cancers	CD19, CD20 or BCMA	Chronic HBV infection	2/12	All received entecavir, tenofovir disoproxil, or lamivudine	Asymptomatic HBV reactivation
			Resolved HBV infection	1/29	No	Asymptomatic HBV reactivation
Cao W 2020 [14]	R/R B-ALL or DLBCL	CD19 and CD22 CAR T cocktail	Chronic HBV infection	1/19	All received prophylactic entecavir	Severe hepatitis and died of septic shock
			Resolved HBV infection	0/37	Only 2 of the 37 received prophylactic entecavir	No HBV reactivation
Ma Y 2021 [22]	One stomach lymphoblastic lymphoma and one R/R DLBCL	CD19 and CD22 CAR T cocktail	Chronic HBV infection	2/2	All received prophylactic entecavir	Both successfully treated with entecavir and tenofovir
Li P 2021 [23]	R/R B-cell malignancies	CD19	Resolved HBV infection	2/30	No antiviral prophylaxis	One asymptomatic HBV reactivation and one severe hepatitis, both successfully treated with entecavir
Kong D 2023 [24]	R/R DLBCL	CD19, CD19 combined with CD20 or CD22, tandem CD19/CD22	Chronic HBV infection	1/6	All received prophylactic entecavir or adefovir combined with entecavir	Hepatic malignant tumor
			Resolved HBV infection	1/25	19 received prophylactic entecavir	One asymptomatic HBV reactivation in no prophylactic group
Fu S 2023 [25]	R/R MM	BCMA	Chronic HBV infection	1/7	6 patients received entecavir and 1 received tenofovir	One developed to liver failure. then died,
			Resolved HBV infection	3/43	No	One hepatitis flare and successfully treated with entecavir, and two asymptomatic HBV reactivation

R/R Relapsed/refractory, *HBV* Hepatitis B virus, *CAR T* Chimeric antigen receptor T-cell, *DLBCL* Diffuse large B-cell lymphoma, *B-ALL* B-cell acute lymphoblastic leukemia, *MM* Multiple myeloma, *BCMA* B cell maturation antigen

with T-cell acute lymphoblastic leukemia (T-ALL) who exhibited high HBV DNA levels. This patient underwent treatment with donor-derived anti-CD7 CAR T-cells, followed by allogeneic hematopoietic stem cell transplantation while receiving continuous antiviral therapy. There was a transient surge in HBV DNA levels observed two weeks following CAR T-cell infusion. However, these levels quickly diminished to a safe range. Impressively, by the 10-month mark following CAR T-cell reinfusion (which was 8 months after transplantation), the patient achieved complete remission with undetectable HBV DNA levels [27]. This case underscores the significance of not overlooking the possibility of HBV reactivation in the context of CAR T-cell therapy for different malignancies beyond B-cells or plasma cells.

In addition, although higher serum interleukin-6 had been observed in patients with chronic HBV infection when receiving CAR T-cell therapy, there is no clear evidence that HBV infection affects the safety or efficacy of CAR T-cell therapy [17]. Both animal studies and clinical studies have shown that HBV infection did not increase the incidence or severity of hepatotoxicity, cytokine release syndrome (CRS), or neurotoxicity during CAR T-cell therapy and did not compromised the activity and clinical efficacy of CAR T-cells [14, 18, 24, 25].

Taken together, these findings collectively underscore the indispensable and efficacious role of NAs prophylaxis in averting HBV reactivation among patients with concomitant chronic HBV infection or resolved HBV infection when undergoing CAR T-cell therapy. Importantly, it appears that the presence of chronic or resolved HBV infection does not impair the safety or efficacy of CAR T-cell therapy. Given the retrospective nature and limited scale of these studies, validation in multicenter prospective trials is warranted.

2 Prevention and Treatments of HBV reactivation during CAR T-cell therapy

2.1 Identification of high-risk populations

HBV serological markers including HBsAg, anti-hepatitis B surface antigen (HBsAb) and anti-hepatitis B core antigen (HBcAb), HBV DNA, and liver function indexes (alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin) should be routinely assessed in patients with hematologic malignancies who receive CAR T-cell therapy. To effectively mitigate the risk of HBV reactivation in these patients, a comprehensive evaluation of risk factors is crucial, guiding the adoption of appropriate prevention and treatment strategies (Fig. 1). Notably, both HBsAg positivity and HBV DNA positivity represent virological risk factors for HBV reactivation. Patients with either chronic HBV infection or resolved HBV infection who test positive for HBV DNA should receive prophylactic NAs therapy before initiating CAR T-cell therapy. It's essential to recognize that even HBV DNA-negative patients with resolved HBV infection must adopt a preemptive treatment approach, as lethal HBV reactivation can still occur following CAR T-cell infusion [19]. In patients with resolved HBV infection, baseline HBsAb seronegativity may serve as a potential risk factor for HBV reactivation, particularly in the absence of antiviral prophylaxis [23]. Additionally, an HBsAb titer of 56.48 IU/ml has been identified as a critical threshold for predicting HBV reactivation, a finding validated in both rituximab-containing chemotherapy and CAR T-cell therapy [20, 28]. HBcAb represents another important biomarker, with a cutoff value of 6.41 IU/ml serving as a cautionary indicator of potential HBV recurrence [29]. Furthermore, the presence of HBeAg positivity is considered a risk factor for reactivation and is associated with elevated viral loads and infectivity levels [15].

2.2 Prophylactic NA therapy

The aforementioned populations with a high risk of HBV reactivation should receive highly potent and low-resistance prophylactic NAs before undergoing CAR T-cell therapy. These NAs include entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate tablets (TAF). Commencement of NA treatment typically initiates one week before, or at the latest, concurrently with prechemotherapy procedures. Currently, most guidelines recommend that patients with hematologic malignancies should receive prophylactic NAs for 12–18 months after immunochemotherapy. Because the sustained duration of B lymphocyte depletion is not consistent between different individuals after receiving a CAR T-cell infusion, the course of prophylactic NAs should be determined by the duration of B lymphocyte depletion in patients [30]. We recommend monitoring the levels of peripheral blood lymphocyte subpopulations and serum immunoglobulins (IgG, IgM, and IgA) in patients with prophylactic NAs. Prophylactic NAs should be given at least 12–18 months after the levels of peripheral blood B lymphocytes and serum immunoglobulins are restored.

2.3 Monitoring and treatment of HBV reactivation

While undergoing NAs treatment, it is crucial to maintain regular monitoring of HBV DNA levels, HBV serological markers, and liver function. Monitoring intervals should occur at least every one to three months, ensuring early intervention when necessary. HBV reactivation often occurs within 6 months after CAR T-cell infusion,

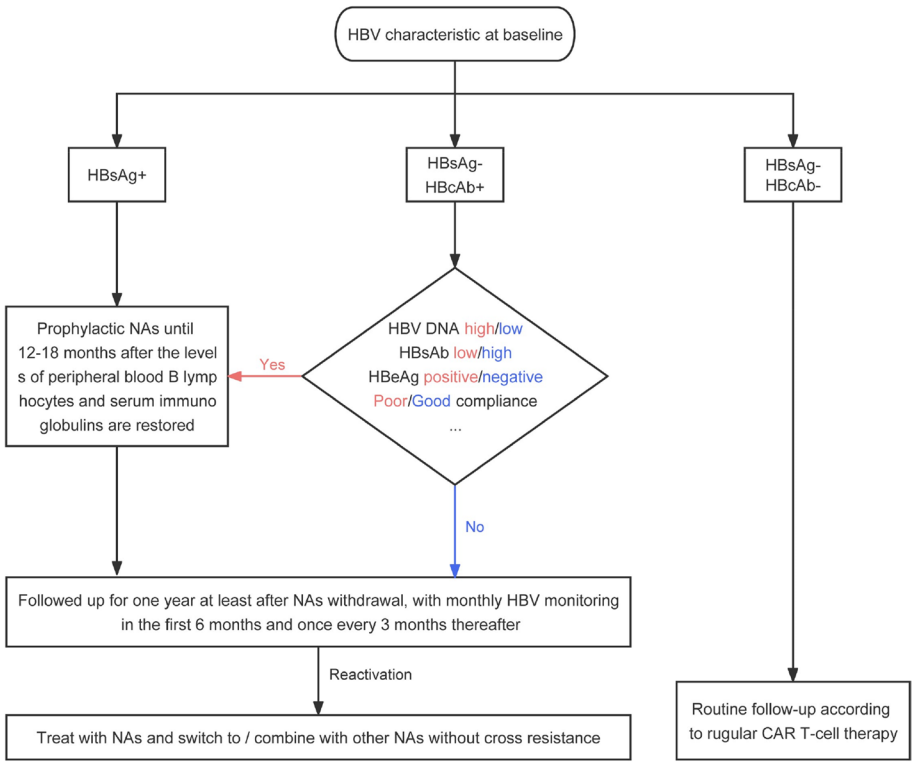

Fig. 1 Prevention and management strategies of HBV reactivation in CAR T-cell therapy. The necessity for prophylactic Nucleotide Analogue (NAs) treatment hinges upon the baseline HBV status of patients prior to CAR T-cell reinfusion. Patients with chronic HBV infection (HBsAg +) or resolved HBV infection (HBsAg- HBcAb +) who exhibit high-risk characteristics (such as a low HBsAb titer or the presence of positive HBeAg) should continue prophylactic NAs until 12–18 months after the restoration of peripheral blood B lymphocytes and serum immunoglobulin levels. HBV status should be monitored regularly until more than one year after NAs withdrawal, with monthly HBV monitoring in the first 6 months and once every 3 months thereafter. In the event of HBV recurrence, immediate initiation of antiviral therapy with NAs that do not share cross-resistance is paramount. CAR T-cell: chimeric antigen receptor T-cell; NAs: nucleotide analogs. HBsAg: hepatitis B surface antigen; HBsAb: anti-hepatitis B surface antigen; HBcAb: anti-hepatitis B core antigen; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus

during which the above indicators should be monitored monthly and once every three months thereafter. Because HBV reactivation can still recur after discontinuation of NAs, the above indicators should continue to be monitored for 12 months after NA withdrawal, at a frequency of once every one to three months, especially within six months. For patients with resolved HBV infection who receive preemptive treatment, a similar monitoring regimen is advised [18, 31]. This vigilant monitoring approach is essential for maintaining patient safety and addressing any potential HBV reactivation promptly.

If HBV reactivation is suspected, prompt assessment and treatment protocols should be initiated to prevent the occurrence of fatal acute liver failure. For patients who have not received prophylactic NAs, immediate initiation of NAs therapy, even before confirmation of HBV reactivation, is essential to prevent further increase in HBV DNA copies. In cases where HBV reactivation occurs despite prophylactic NAs use, the possibility of viral resistance mutations should be considered, particularly in patients with lamivudine resistance who are more susceptible to entecavir resistance mutations [32, 33]. Alongside drug-resistance gene testing, adjustments to antiviral treatment regimens should be made, including switching to or adding NAs drugs with no cross-resistance, such as ETV, TDF and TAF. However, potential adverse reactions associated with NAs should be monitored. Multidisciplinary therapy may be initiated if necessary. Additionally, based on the patient's liver function, hepatoprotective drugs and supportive treatments should be administered accordingly.

3 Conclusion

CAR T-cell therapy represents a groundbreaking advancement in the treatment of hematological malignancies and is gaining increasing traction. However, it is essential to conduct meticulous evaluations of the safety and efficacy of CAR T-cell therapy, especially in specific

patient subgroups. A substantial portion of patients with hematologic malignancies presents concurrent chronic or resolved HBV infection. Consequently, when administering CAR T-cell therapy to such individuals, a heightened awareness of the risk of HBV reactivation is paramount. The continuous prophylactic use of NAs has demonstrated its effectiveness in curbing HBV recurrence. Equally important is the early identification of high-risk populations and the implementation of long-term, regular monitoring of HBV DNA levels. In addition, based on several independent clinical studies, we concluded that the infection status of HBV does not compromise the safety and efficacy of CAR T-cell therapy. Therefore, CAR T-cell therapy for patients with hematological malignancies and concomitant HBV infection holds significant promise.

Abbreviations

B-ALL	B-cell acute lymphoblastic leukemia
BCMA	B cell maturation antigen
CAR	Chimeric antigen receptor
CRS	Cytokine release syndrome
DLBCL	Diffuse large B-cell lymphoma
ETV	Entecavir
HBcAb	Anti-hepatitis B core antigen
HBeAg	Hepatitis B e antigen
HBsAb	Anti-hepatitis B surface antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
MM	Multiple myeloma
NAs	Nucleotide analogs
NHL	Non-Hodgkin lymphoma
R/R	Relapsed/refractory
T-ALL	T-cell acute lymphoblastic leukemia

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References

1. The consensus on the prophylaxis and treatment of HBV reactivation in B or plasma cell-directed CAR-T cell therapy (2021). Zhonghua Xue Ye Xue Za Zhi. 2021;42(6):441–446.
2. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015;386(10003):1546–55.
3. Global, regional, and national burden of hepatitis B, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Gastroenterol Hepatol. 2022;7(9):796–829.
4. Revill PA, Tu T, Netter HJ, Yuen LKW, Locarnini SA, Littlejohn M. The evolution and clinical impact of hepatitis B virus genome diversity. Nat Rev Gastroenterol Hepatol. 2020;17(10):618–34.
5. Kim M, Lee YK, Park B, Oh DJ, Choi HG. Hepatitis virus B and C infections are associated with an increased risk of non-Hodgkin lymphoma: A nested case-control study using a national sample cohort. J Med Virol. 2020;92(8):1214–20.
6. Ren W, Ye X, Su H, et al. Genetic landscape of hepatitis B virus-associated diffuse large B-cell lymphoma. Blood. 2018;131(24):2670–81.
7. 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.
8. Yeo W, Chan TC, Leung NW, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol. 2009;27(4):605–11.
9. Papatheodoridis GV, Lekakis V, Voulgaris T, et al. Hepatitis B virus reactivation associated with new classes of immunosuppressants and immunomodulators: A systematic review, meta-analysis, and expert opinion. J Hepatol. 2022;77(6):1670–89.
10. Evens AM, Jovanovic BD, Su YC, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. Ann Oncol. 2011;22(5):1170–80.
11. Seto WK, Chan TS, Hwang YY, et al. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. J Clin Oncol. 2014;32(33):3736–43.
12. Wang B, Mufti G, Agarwal K. Reactivation of hepatitis B virus infection in patients with hematologic disorders. Haematologica. 2019;104(3):435–43.
13. Mustafayev K, Torres H. Hepatitis B virus and hepatitis C virus reactivation in cancer patients receiving novel anticancer therapies. Clin Microbiol Infect. 2022;28(10):1321–7.
14. Cao W, Wei J, Wang N, et al. Entecavir prophylaxis for hepatitis B virus reactivation in patients with CAR T-cell therapy. Blood. 2020;136(4):516–9.
15. 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.
16. Wang Y, Liu Y, Tan X, et al. Safety and efficacy of chimeric antigen receptor (CAR)-T-cell therapy in persons with advanced B-cell cancers and hepatitis B virus-infection. Leukemia. 2020;34(10):2704–7.
17. Strati P, Nastoupil LJ, Fayad LE, Samaniego F, Adkins S, Neelapu SS. Safety of CAR T-cell therapy in patients with B-cell lymphoma and chronic hepatitis B or C virus infection. Blood. 2019;133(26):2800–2.
18. Lai P, Chen X, Qin L, et al. The efficacy and safety of CAR-T cell therapy in patients with refractory ALL and concomitant HBV infection. Leukemia. 2020;34(10):2790–3.
19. Cui R, Lyu C, Li Q, et al. Humanized anti-CD19 chimeric antigen receptor-T cell therapy is safe and effective in lymphoma and leukemia patients with chronic and resolved hepatitis B virus infection. Hematol Oncol. 2021;39(1):75–86.
20. Liu W, Huang W, Wang M, et al. Risk of hepatitis B reactivation is controllable in patients with B-cell lymphoma receiving anti-CD19 CAR T cell therapy. Br J Haematol. 2020;191(1):126–9.
21. Han L, Zhou J, Zhou K, et al. Safety and efficacy of CAR-T cell targeting BCMA in patients with multiple myeloma coinfected with chronic hepatitis B virus. J Immunother Cancer. 2020;8(2):e000927.
22. Ma Y, Yang L, Bao Y, Yang Y, Chen L, Zheng M. Case Report: Post-CAR-T Infusion HBV Reactivation in Two Lymphoma Patients Despite Entecavir Preventive Therapy. Front Immunol. 2021;12: 751754.

23. Li P, Zhou L, Ye S, et al. Risk of HBV reactivation in patients with resolved HBV Infection Receiving Anti-CD19 chimeric antigen receptor T Cell therapy without antiviral prophylaxis. Front Immunol. 2021;12: 638678.
24. Kong D, Ping N, Gao X, et al. Efficacy and safety of chimeric antigen receptor T cell therapy in relapsed refractory diffuse large B-cell lymphoma with different HBV status a retrospective study from a single center. Front Immunol. 2023;14:1200748.
25. Fu S, Zhang Q, Jing R, et al. HBV reactivation in patients with chronic or resolved HBV infection following BCMA-targeted CAR-T cell therapy. Bone Marrow Transplant. 2023;58(6):701–9.
26. Wei J, Zhu X, Mao X, Huang L, Meng F, Zhou J. Severe early hepatitis B reactivation in a patient receiving anti-CD19 and anti-CD22 CAR T cells for the treatment of diffuse large B-cell lymphoma. J Immunother Cancer. 2019;7(1):315.
27. Li Z, Meng F, Li J, Wu T. Donor-Derived CD7 CAR-T therapy followed by allogeneic hematopoietic stem cell transplantation for acute T-Lymphocytic leukemia associated with hepatitis B: A case report. Front Immunol. 2022;13: 931452.
28. Yang HC, Tsou HH, Pei SN, et al. Quantification of HBV core antibodies may help predict HBV reactivation in patients with lymphoma and resolved HBV infection. J Hepatol. 2018;69(2):286–92.
29. Nishida T, Matsubara T, Yakushijin T, Inada M. Prediction and clinical implications of HBV reactivation in lymphoma patients with resolved HBV infection: focus on anti-HBs and anti-HBc antibody titers. Hepatol Int. 2019;13(4):407–15.
30. Mueller KT, Maude SL, Porter DL, et al. Cellular kinetics of CTL019 in relapsed/refractory B-cell acute lymphoblastic leukemia and chronic lymphocytic leukemia. Blood. 2017;130(21):2317–25.
31. Hwang JP, Feld JJ, Hammond SP, et al. Hepatitis B virus screening and management for patients with cancer prior to therapy: ASCO provisional clinical opinion update. J Clin Oncol. 2020;38(31):3698–715.
32. Fischer KP, Gutfreund KS, Tyrrell DL. Lamivudine resistance in hepatitis B: mechanisms and clinical implications. Drug Resist Updat. 2001;4(2):118–28.
33. Lee JH, Cho Y, Lee DH, et al. Prior exposure to lamivudine increases entecavir resistance risk in chronic hepatitis B Patients without detectable lamivudine resistance. Antimicrob Agents Chemother. 2014;58(3):1730–7.

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