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Original Article

Low incidence of hepatitis B virus reactivation in patients with hematological malignancies receiving novel anticancer drugs: A report from a high epidemic area and literature review

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Abbreviations: HBV, hepatitis B virus; HBV-R, HBV-reactivation; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; PAT, prophylactic antiviral treatment; BTK, Bruton tyrosine kinase; PI3K, phosphoinositide 3-kinase; CAR-T, chimeric antigen receptor T; ICI, immune checkpoint inhibitor; CT, chemotherapy; ICT, immunochemotherapy; EpiD, epigenetic drug.

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KEYWORDS
Hematological malignancy;
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Abstract *Background:* More and more novel anticancer drugs have been approved for patients with hematological malignancies in recent years, but HBV reactivation (HBV-R) data in this population is very scarce. This study aimed to evaluated HBV-R risk in patients with hematological malignancies receiving novel anticancer drugs.
Methods: HBV markers and serum HBV DNA levels of patients with hematological malignancies receiving novel anticancer drugs in a tertiary cancer hospital were retrospectively collected. HBV-R risk in the whole cohort and subgroups was described. The relevant literature was reviewed to make a pooled analysis.
Results: Of 845 patients receiving novel anticancer drugs, 258 (30.5%) were considered at risk for HBV-R. The median duration of exposure to novel drugs was 5.6 (0.1—67.6) months. The incidence of HBV-R was 2.1% in patients with past HBV infection without prophylactic antiviral treatment (PAT) and 1.2% in all patients at risk of HBV-R. In a pooled analysis of 11 studies with 464 patients, the incidence of HBV-R was 2.4% (95% CI: 1.3—4.2) in all at-risk patients receiving novel anticancer drugs and 0.6% (95% CI: 0.03—3.5) in patients with anticancer drugs plus PAT. The incidence of death due to HBV-R was 0.4% (95% CI: 0.1—1.6) in all at-risk patients and 18.2% (95% CI: 3.2—47.7) in patients with HBV-R.
Conclusion: Most episodes of HBV-R are preventable, and most cases with HBV-R are manageable. We recommend that novel anticancer drugs should not be intentionally avoided when treating cancer patients with HBV infection.

Introduction

Hepatitis B virus (HBV) can cause life-threatening liver disease. Although HBV vaccines and anti-HBV virus drugs are available worldwide today, HBV infection remains a global health problem. Approximately 2 billion people have past or present HBV infection, and around 240 million people are chronically infected.[1] China is a high HBV prevalence region. The national hepatitis sero-epidemiological survey in 1992 revealed that the prevalence of hepatitis B surface antigen (HBsAg) in individuals aged 1—59 years was 9.75%, and the second survey in 2006 showed it had dropped to 7.18% due to planned vaccination of newborns.[2]

HBV-infected patients with hematological malignancies are at risk for HBV reactivation (HBV-R) when receiving immunosuppressive anticancer agents, such as cytotoxic chemotherapeutics, corticosteroids, especially anti-CD20 monoclonal antibody-based immunochemotherapy. It is recommended that all patients be screened for HBV infection, including HBsAg and hepatitis B core antibody (HBcAb) testing, before starting immunosuppressive anticancer therapies. If HBsAg or HBcAb is positive, further HBV DNA test should be carried out. There are two strategies for preventing HBV-R: prophylactic or on-demand antiviral treatment. Generally, for HBsAg-positive patients, antiviral drugs should be initiated before immunochemotherapy regardless of serum HBV DNA levels; in patients with negative HBsAg but positive HBcAb, liver function and HBV DNA should be monitored regularly, and antiviral drug should be started immediately when HBV reactivation is detected. Prophylactic antiviral treatment (PAT) is another option for HBsAg-negative and HBcAb-positive patients.[3]

HBV-R risk has been well evaluated in the rituximab era. In recent years, an increasing number of novel anticancer agents, such as Bruton tyrosine kinase (BKT) inhibitor (BTKi), phosphoinositide 3-kinase (PI3K) inhibitor (PI3Ki), and BCL2 inhibitor, have been approved or under intensive investigation for the treatment of hematological malignancies, most of which have immunosuppressive effects. However, to date, there are very scarce data on HBV-R in patients treated with these novel drugs. One reason is that the majority of clinical trials of these novel drugs have excluded HBV-infected patients due to the potential risk of HBV-R. In practice, it was not uncommon that novel anticancer drugs were delayed or intentionally avoided in the management of patients with hematological malignancy and HBV infection, which might lead to compromised clinical outcomes. Therefore, this study aimed to evaluate HBV-R risk in patients with hematological malignancies receiving novel anticancer drugs in an epidemic area.

Methods

Study design and patient selection

We performed a retrospective analysis of patients with hematological malignancies treated at Zhengzhou University Affiliated Cancer Hospital, a tertiary cancer hospital in China, to evaluate HBV-R risk beyond cytotoxic agents and rituximab (or its biosimilars). Patients treated with small molecule drugs, monoclonal antibodies (excluding anti-CD20 antibodies), bispecific antibodies, antibody—drug conjugates, and chimeric antigen receptor T (CAR-T) cells were included. Patients receiving immune checkpoint

inhibitors (ICIs) were excluded, because ICIs are not immunosuppressive agents. On the contrary, ICIs are under investigation to treat HBV infection.[4—6] Except for BTKi, most of these anticancer drugs were used in early-stage clinical trials in our hospital in the past few years, so this study included both real-world patients and clinical trial participants.

Detection of HBV serologic markers and DNA

Although assessment schedules varied by patient, typically, HBV DNA was tested every one to three months while HBV serologic markers were tested every three to six months. Serological HBV markers including serum HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb, were detected by electrochemiluminescent immunoassay (ECLIA, Roche diagnostics), chemiluminescent microparticle immunoassay (CMIA, Autobio Diagnostics Co. Ltd., China), or enzyme-linked immunosorbent assay (ELISA, Autobio Diagnostics Co. Ltd., China). For HBsAb and HBcAb detection, these assays targeted both IgG and IgM. The definitions of positivity were as following: (1) for ECLIA, HBsAb $>$ 10 IU/L, HBcAb $<$ 1 COI; (2) for CMIA, HBsAb $>$ 10 IU/L, HBcAb $>$ 0.7 PEIU/mL; (3) for ELISA, HBsAb $>$ 1 S/CO, HBcAb $<$ 1 S/CO. Only data generated in our hospital were included in analysis. In consecutive testing results, if an abnormal value appeared transiently and was closed to cut-off, it was not considered positive to reduce laboratory errors. HBV DNA in serum was measured using a quantitative, real-time polymerase chain reaction (PCR) assay (Sansure Biotech Co. Ltd. China) with a lower limit of quantitation of 5 IU/mL.

Definition of HBV-R

Different guidelines define HBV-R differently, but their general principles are similar. Chronic HBV infection is defined as HBsAg positive for more than 6 months. Past HBV infection (also called resolved HBV infection or occult HBV infection) is defined as HBsAg negative and HBcAb positive, regardless of the status of antibody to HBsAg (HBsAb).[7,8] This study adopted the definition of HBV-R from the American Society of Clinical Oncology (ASCO) 2020 update (same as the American Association for the Study of Liver Diseases 2018 guideline). In patients with chronic HBV infection, HBV-R is considered if any of the following criteria are met: $\geq$10, 000 IU/mL if baseline DNA is unavailable; $\geq$1000 IU/mL if baseline DNA is undetectable; or $\geq$100-fold increase if baseline DNA is detectable. In patients with past HBV infection, HBV-R is considered if any of the following criteria are met: development of detectable HBV DNA or reappearance of HBsAg (also known as reverse seroconversion).[7]

Literature review

The following search strategy was used to identify literatures on patients with hematological malignancies and HBV-R through Pubmed and Embase regardless of publishing year: HBV reactivation [AB] AND (hemato* malignancy [AB] hemato* neoplasms [AB] OR hemato* tumour [AB] OR lymphoma [AB] OR leukemia [AB] OR myeloma [AB] OR waldenström's macroglobulinaemia [AB] OR myelodysplastic syndrome [AB] OR myeloproliferative neoplasm OR myeloid neoplasms [AB] OR mastocytosis [AB] OR dendritic cell neoplasm [AB] OR histiocytic neoplasm [AB]) NOT (rituximab [TI] OR anti-CD20 antibody [TI]). Retrieved literatures associated with novel anticancer drugs were manually picked out for analysis. The references cited by selected literatures were also traced.

Statistical analysis

The incidence of HBV-R patients was statistically described. Exposure time was calculated from the date of novel anticancer drug initiation to the date of drug discontinuation or the last dose recorded in the medical records. Due to the time required from initiation of anticancer drugs to occurrence of HBV-R, only those patients with follow-up $\geq$ 3 months after drug therapy initiation were included in the HBV-R risk analysis. GraphPad Prism (version 9) was used in statistical analysis and figure preparation.

Ethics statement

This study was approved by the Institutional Review Board of Affiliated Cancer Hospital of Zhengzhou University, and written informed consent was obtained from all patients at their first admission. Furthermore, this study was conducted in accordance with the Helsinki Declaration.

Results

Patient characteristics

From February 1, 2017 to June 30, 2022, a total of 845 patients with hematological malignancies receiving novel anticancer drugs were retrieved from the electronic medical record system, of whom 66 (7.8%) were HBsAg positive, 242 (28.6%) were HBcAb positive, 279 (33.0%) were isolated HBsAb positive, 1 (0.1%) was isolated HBeAb positive, 253 (29.9%) were negative for all 5 HBV markers, and 4 (0.5%) had no available data of HBV markers. A total of 308 (36.4%) HBsAg or HBcAb positive patients were considered to have HBV-R risk, of whom 50 cases with $<$3 months follow-up were excluded (no HBV-R was observed in these patients), and the remaining 258 patients (30.5%) were included in HBV-R risk analysis (Fig. 1). Their clinical characteristics are summarized in Table 1.

Treatment and HBV-R

Except for BTKi, other novel drugs mentioned in the Methods have not yet been marketed (or have just been marketed) in mainland China, and clinical trials of these novel drugs have mostly excluded HBV-infected patients, so the number of patients receiving other novel anticancer drugs was relatively small. In a portion of patients (58.1%), these novel drugs were used in combination with other anticancer agents (partner drugs), involving cytotoxic chemotherapy (CT), immunochemotherapy (ICT), epigenetic drugs (EpiD, referring to DNA methyltransferase or

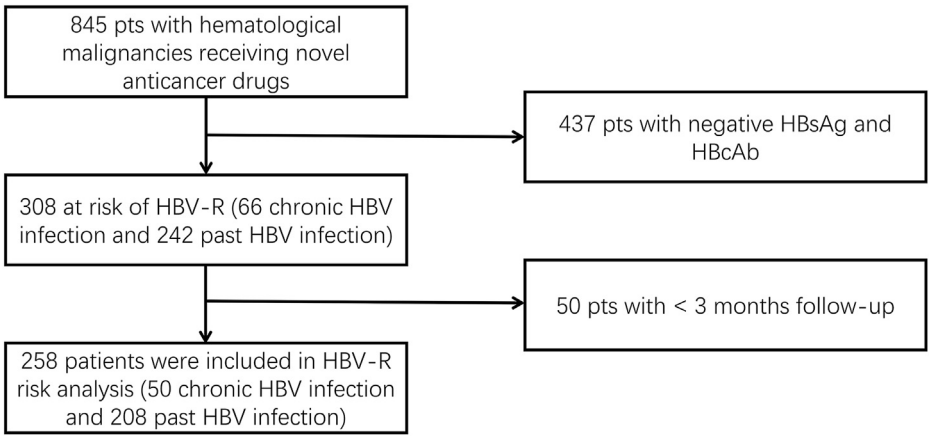

Figure 1. Patient flow diagram.

Table 1 Characteristics of 258 patients with past or chronic HBV infection.

Parameter	N (%)
Gender	
Male	160 (62.0)
Female	98 (38.0)
Age (median)	62.5 (28—93)
Patient type	
Clinical trial participants	93 (36.0)
Real world patients	165 (64.0)
Type of HBV infection	
Chronic HBV infection (HBsAg+)	50 (19.4)
Past HBV infection (HBcAb+)	208 (80.6)
HBV DNA at baseline	
Detectable	17 (6.6)
Undetectable	241 (93.4)
Prophylactic antiviral treatment (PAT)	
Yes	112 (43.4)
No	146 (56.6)
Diagnosis	
B-cell malignancies[a]	185 (71.7)
Myeloid neoplasmas and other hematological malignancies[b]	56 (21.7)
T/NK-cell lymphomas	17 (6.6)

[a] The subtypes included diffuse large B-cell lymphoma (n = 74), chronic lymphocytic lymphoma/small lymphocytic lymphoma (n = 40), mantal cell lymphoma (n = 37), and other indolent B-cell lymphomas (follicular lymphoma, marginal zone lymphoma, or Waldenström's macroglobulinaemia; n = 25).
[b] The subtypes included acute myelocytic leukemia (n = 49), multiple myeloma, acute lymphoblastic leukemia, myelodysplastic syndromes, and chronic myeloid leukemia (n = 16).

histone demethylase inhibitors), and other drugs (lenalidomide and tyrosine kinase inhibitors) (Table 2). The median duration of exposure to these novel anticancer drugs was 5.6 (0.1—67.6) months, and the median follow-up after initiation of these drugs was 8.6 (3.1—67.6) months. In addition, 40 (15.5%) patients received ≥ two lines of novel anticancer drugs.

More specifically, 47 out of 50 (94.0%) patients with chronic HBV infection and 65 out of 208 (31.3%) patients with past HBV infection started entecavir antiviral therapy before or at the beginning of anticancer treatment. Further, 15 out of 50 (30.0%) patients with chronic HBV infection and 2 out of 208 (1.0%) patients with past HBV infection had detectable HBV DNA at baseline. The median number of HBV DNA was 9100 (133—42,700,000) IU/mL. All of these patients with detectable HBV DNA at baseline received entecavir before or at the beginning of anticancer treatment. After anticancer treatment, no HBV-R was observed in patients receiving PAT.

However, HBV-R occurred in 3 patients with past HBV infection who did not receive PAT. All of these 3 patients had normal liver function and undetectable HBV DNA at baseline. The first patient with peripheral T-cell lymphoma (PTCL) had previously been treated with CT, anti-CD30 antibody—drug conjugate, and anti-CD52 antibody. HBV-R was observed 3.9 months after JAK1 inhibitor initiation. At that time, the patient's HBV DNA was 203 IU/mL, the liver function was normal, and the HBV markers maintained HBsAg-negative/HBcAb-positive. Therapeutic entecavir was given immediately. After 3 weeks of entecavir treatment, HBV DNA became undetectable. The second patient with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) developed HBV-R 3.7 months after BTKi initiation. In addition to 5.8×10^7 IU/mL of HBV DNA, the patient exhibited HBsAg reappearance, elevated liver enzymes (ALT 132 U/L and AST 123 U/L), and normal bilirubin. After 3 weeks of entecavir treatment, HBV DNA decreased 100-fold and liver enzymes returned to normal. The third male patient had the same disease and treatment as the second patient. He received two cycles of cyclophosphamide plus fludarabine before BTKi therapy. Detectable HBV DNA (178 IU/mL) and reappeared HBsAg were observed 5 months after initiation of the BTKi despite normal liver function. Entecavir was subsequently administered, and HBV DNA was undetectable two weeks later.

Briefly, the incidence of HBV-R was 2.1% (3/143, 95% CI: 0.6—6.0) in patients with past HBV infection who did not receive PAT and 1.2% (3/258, 95% CI: 0.3—3.4) in all patients at risk for HBV-R.

Table 2 Treatment and HBV reactivation in 258 patients with past or chronic HBV infection.

Drug	N	Partner drugs	Chronic HBV infection (HBsAg+)		Past HBV infection (HBcAb+)	
			PAT	W/O PAT	PAT	W/O PAT
BTK inhibitors	116	ICT 51; CT 13; other drugs 4	32	1	33	50 (2)[a]
BCL2 inhibitors	70	ICT 2; CT 5; EpiD 50; other drugs 3	5	1	15	49
PI3K inhibitors	24	EpiD 2	3	1	5	15
Other small molecule drugs (targeting EZH2, XPO1, PKCβ, CDK9, JAK1, or SYK)	15	ICT 4; CT 1; EpiD 1	4	0	3	8 (1)[a]
Antibody—drug conjugates (targeting CD30 or CD79)	13	ICT 8; CT 2	1	0	3	9
Bispecific antibodies (targeting CD19/CD3, CD20/CD3, or CD47/CD20)	9	CT 2	0	0	2	7
Monoclonal antibodies (targeting CD38, CD47, or CD52)	5	ICT 1; other drugs 1	1	0	0	4
CAR-T[b]	6	—	1	0	4	1

[a] The number of patients who developed HBV-R is shown in parentheses.
[b] Nine other patients with HBV infection receiving CAR-T therapy in our hospital have been previously reported.[9] The 6 patients included here do not overlap with the 9 reported.
PAT, prophylactic antiviral treatment; W/O, without; ICT, immunochemotherapy; CT, chemotherapy; EpiD, epigenetic drugs.

HBV-R in isolated HBsAb-positive patients

In 279 isolated HBsAb-positive patients, HBsAg reappeared in 3 (1.1%, 95% CI: 0.3—3.1) patients, including 2 with elevated serum HBV DNA. The first patient was a 73-year-old male with CLL/SLL who received a BTKi in combination with CT. HBsAg reappeared with positive HBcAb and HBeAb 2.2 months after starting anticancer treatment. Serum HBV DNA was 4.47×10^6 IU/mL and liver enzymes were elevated (ALT 571 U/L and AST 279 U/L). After one month of entecavir treatment, serum HBV DNA declined to 542 IU/mL and liver enzymes returned to normal levels. Three months later, serum HBV DNA became undetectable. The second patient was a 65-year-old female with CLL/SLL who received a BTKi plus ICT. Eight months after starting the combined anticancer treatment, she was positive for HBsAg, HBcAb, and HBeAg, with detectable serum HBV DNA of 4.79×10^7 IU/mL, but had normal liver function. Entecavir was given, but the patient was lost to follow-up thereafter. The third was an 11-year-old boy diagnosed with acute myelocytic leukemia (AML). He tested positive for HBsAg, HBcAb, and HBeAg and had undetectable serum HBV DNA 1.6 months after starting BCL2 inhibitor plus epigenetic drugs. His treatment was discontinued due to unresponsiveness. The supplementary file 1 provides the titers (or S/CO values) of HBsAb and HBcAb of these patients at baseline and at the time of HBV-R (Patient ID 1 to 3). Including these 3 cases, the incidence of HBV-R in all patients in our whole cohort was 0.7% (6/845, 95% CI: 0.3—1.5).

In addition to HBV-R, HBcAb reappearance was observed in 6.8% (19/279, 95% CI: 4.4—10.4) of isolated HBsAb-positive patients, but none of them had detectable HBV-DNA. The supplementary file 1 provides the titers (or S/CO values) of HBsAb and HBcAb of these patients at baseline and at the time of HBV-R (Patient ID 4 to 22).

Discussion

With the increasing availability of novel anticancer drugs for patients with hematological malignancies, there is a need to re-examine HBV-R risk in patients with chronic or past HBV infection, as the incidence of HBV-R in this population is largely unknown. Herein we performed a literature review to gain a better understanding of the incidence of HBV-R. As a result, apart from several case reports describing the occurrence of HBV-R in patients receiving BTK inhibitors,[10—15] CAR-T cell therapy,[16—18] anti-CD30 antibody—drug conjugate,[19] anti-CD38 antibody,[20,21] anti-

Table 3 Reported incidence of HBV reactivation in patients with hematological malignancies receiving novel anticancer drugs.

Cancer and reference	Novel anticancer drug	Pts at risk of HBV-R	Median exposure time[a]	Definition of HBV-R	Chronic HBV infection		Past HBV infection		HBV-R-related death (%)
					PAT	W/O PAT	PAT	W/O PAT	
CLL/SLL[28]	BTKi	7	NA	AGA 2015 guideline[b]	0	0	0	7	0
CLL/SLL[29]	BTKi	12	NA	AGA 2015 guideline	0	0	0	12 (1)[c]	0
Hematological malignancies[30]	BTKi	21	9.5 m	Development of HBV DNA >100 IU/mL on two consecutive tests	0	0	0	21 (2)[c]	0
CLL/SLL[31]	BTKi	36	28.0 m	APASL 2016 guideline[d]	0	0	2	34	0
B-cell malignancies[32]	CAR-T	30	12.0 m	Elevation of HBV DNA ≥100 IU/mL for two consecutive tests	0	0	0	30 (2)[c]	0
B-cell malignancies[25]	CAR-T	17	10 m	Elevation of HBV DNA levels to more than 1000 IU/mL and/or HBsAg reverse seroconversion	6	0	5	6	0
B-cell malignancies[26]	CAR-T	55	NA	AASLD 2018 guideline	19 (1)[c,e]	0	2	34	1 (1.8)
DLBCL and ALL[27]	CAR-T	20	NA	AASLD 2018 guideline	5	0	2	13 (1)[c,e]	1 (5.0)
MM[9]	CAR-T	9	9.8 m	1) Loss of HBsAb and reoccurrence of HBsAg in HBsAg- and/or HBsAb + patients and 2) increase of HBV DNA level by 10-fold or an absolute count of HBV DNA reaching 1×10^9 copies/mL	1	0	2	6 (1)	0
MM[33]	Daratumumab	—	2.5 cycles	KASL 2019 guidline[f]	0	0	0	?[g] (6)[c,e]	1 (?)
Hematological malignancies (this study)	Multiple novel drugs	258	5.6 m	ASCO 2020 update (same as the AASLD 2018 guideline)	47	3	65	143 (3)[c]	0

[a] For patients receiving CAR-T therapy, the follow-up time was the exposure time.

[b] Definition of HBV-R in AGA 2015 guideline: patients with chronic HBV infection who meet any of the following criteria: 1) de novo detectable DNA in patients with undetectable HBV DNA at baseline; 2) ≥10-fold increase in patients with detectable HBV DNA at baseline; or patients with past HBV infection who experience reverse seroconversion to HBsAg-positive status.

[c] Numbers in parentheses indicate the number of patients experiencing HBV-R.

[d] Definition of HBV-R in APASL 2016 guideline: patients with chronic HBV infection who meet any of the following criteria: 1) de novo detectable HBV DNA to a level of 100 IU/mL in patients with undetectable DNA at baseline; 2) ≥2 log increase in patients with detectable HBV DNA at baseline; 3) ≥20,000 IU/mL in patients without HBV DNA data at baseline.

[e] One patient died of HBV-R in each of these studies.

[f] Definition of HBV-R in KASL 2019 guideline: for patients with chronic HBV infection, an increase of HBV DNA by more than 100 times the baseline level; for patients with past HBV infection, seroconversion of HBsAg-negative to positive, or detection of serum HBV DNA from none to positive.

[g] In this study, 61 of 93 patients were evaluated for HBcAb at baseline, of whom 24 were positive, so the exact number of HBcAb-positive patients in the whole cohort was unknown. Data from this study were excluded when analyzing the incidence of HBV-R.

Pts, patients; PAT, prophylactic antiviral treatment; W/O, without; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; BTKi, BTK inhibitor; NA, not available; AGA, American Gastroenterology Association; m, months; APASL, The Asian Pacific Association for the Study of the Liver; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; ALL, acute lymphoblastic leukemia; AASLD, American Association for the Study of Liver Diseases; MM, multiple myeloma; KASL, Korean Association for the Study of the Liver; ASCO, American Society of Clinical Oncology.

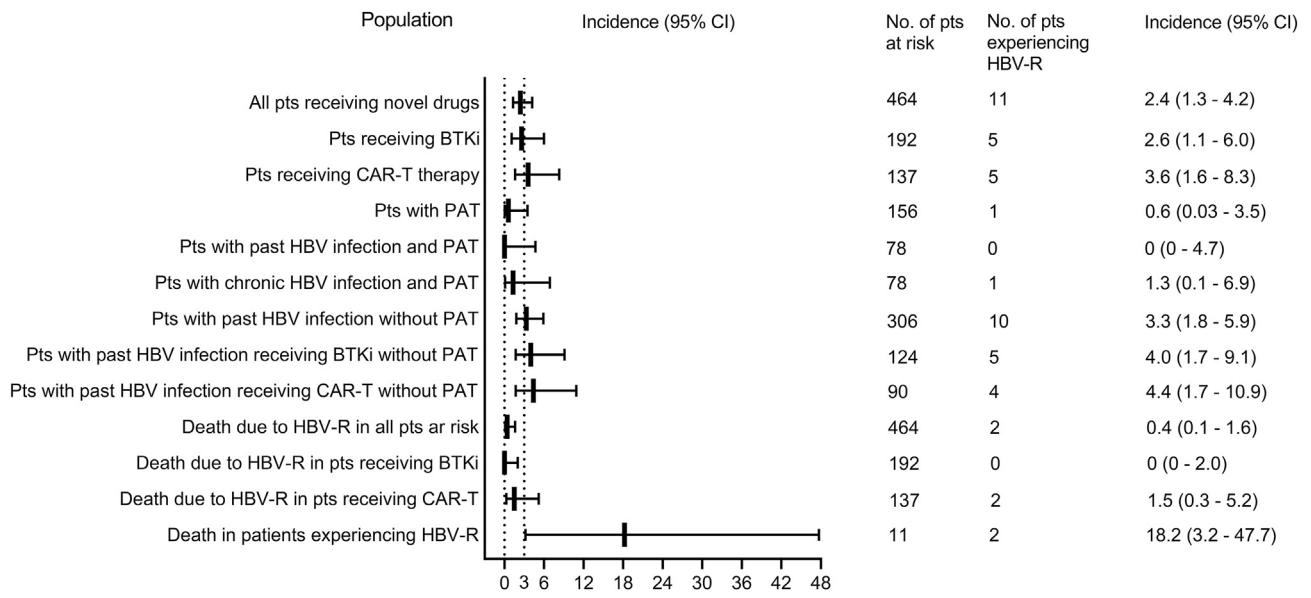

Fig. 2. Pooled incidence of HBV reactivation. Pts, patients; HBV-R, HBV reactivation; BTKi, BTK inhibitor; CAR-T, chimeric antigen receptor T-cell; PAT, prophylactic antiviral treatment.

CD52 antibody,[22] anti-CC chemokine receptor 4 (CCR4) antibody,[23,24] only a few small cohort studies have described the incidence of HBV-R in patients treated with BTKi and CAR-T cell therapies. Data from these studies are summarized in Table 3. Clearly, HBV-R occurred mainly in patients with past HBV infection who did not receive PAT prior to receiving novel anticancer drugs. In these studies, the incidence of HBV-R ranged from 0 to 16.7% in at-risk patients without PAT and from 0 to 11.1% in all at-risk patients. Because the majority of patients included in these studies were clinical trial participants, patients with chronic HBV infection were largely excluded. In fact, only a total of 31 patients with chronic HBV infection were included in 4 studies.[9,25—27] Moreover, all of these patients had undetectable HBV DNA at the beginning of anticancer treatment. Therefore, evaluation of HBV-R risk in patients with chronic HBV infection is most important, especially those with elevated serum HBV DNA.

Similar to previous studies, we found a low incidence of HBV-R in patients with past HBV infection without PAT. These few episodes of reactivation were all well controlled by timely administration of antivirus agents. Unlike previous studies, however, this study included patients receiving more types of novel anticancer drugs, some of which had not been previously reported, such as BCL2 inhibitors, PI3K inhibitors, and bispecific antibodies. Besides, a significant number (n = 50) of patients with chronic HBV infection, especially 17 (15 with chronic HBV infection and 2 with past HBV infection) patients had elevated HBV DNA when starting treatment with these novel drugs. It is also worth mentioning that a considerable proportion of patients in this study received novel anticancer drugs in combination with other immunosuppressive anticancer agents. As a result, of a total of 258 at-risk patients, only 3 (2 receiving a BTKi and 1 receiving a JAK1 inhibitor) without PAT developed HBV-R. Our data show that patients with PAT are at low risk of developing HBV-R, regardless of whether the patient has chronic HBV infection or past HBV infection, elevated or undetectable serum HBV DNA levels at baseline, and novel drugs administered alone or in combination with other immunosuppressive anticancer drugs.

As cumulative data to date were very limited, we performed a pooled analysis of our data and previously published data to gain a better understanding of the incidence of HBV-R. Case reports were excluded from this analysis. As shown in Table 3 and Fig. 2, a low incidence of HBV-R was observed in patients with hematological malignancies receiving novel anticancer drugs, especially in patients with PAT. The vast majority of HBV-R episodes (10/11) occurred in patients without PAT, indicating that most reactivations are preventable. The pooled incidence of HBV-R was 2.4% (95% CI: 1.3—4.2) in all patients at risk from receiving novel anticancer drugs. The incidence of HBV-R in patients with PAT was 0.6% (95% CI: 0.03—3.5). The incidence of HBV-R appears to be relatively higher (>3.0%) in patients without PAT and in patients receiving CAR-T therapy. The pooled incidence of death due to HBV-R was 0.4% (95% CI: 0.1—1.6) in all at-risk patients. Patients who developed HBV-R had a pooled death rate of 18.2% (95% CI 3.2—47.7).

As most of the above-mentioned studies did not include or included a limited number of patients with chronic HBV infection, HBV-R risk in this population needs to be evaluated in more patients. It seems that chronic HBV-infected patients treated with CAR-T are at higher risk of developing HBV-R, but this is inconclusive, as the incidence of HBV-R in chronic HBV-infected patients was only evaluated in a total of 31 patients receiving CAR-T therapy in previous studies (Table 3). The present study included 50 patients with chronic HBV infection, of whom 30.0% had elevated serum HBV DNA, but no cases of HBV-R were observed, suggesting that novel anticancer drugs are applicable to this population. It should be noted that the vast majority of these

patients (94.0%, 47/50) received PAT. In the absence of more convincing data, special attention should be paid to HBV-R in patients with chronic HBV infection receiving CAR-T therapy. For chronic EBV-infected patients receiving CAR-T therapy, it is better to control HBV DNA to undetectable levels before the treatment. In addition, to our knowledge, this study is the first to evaluate HBV-R risk in patients receiving BCL2 inhibitors, PI3K inhibitors, and bispecific antibodies. Despite the limited number of patients included, the absence of HBV-R cases in patients receiving these drugs suggests that they have a low risk of causing HBV-R. The risk of HBV-R is even lower when the cost and harm of the cancer itself are taken into account. We suggest that patients with chronic HBV infection or patients with detectable HBV DNA should be given PAT before initiating novel anticancer drugs. In patients with past HBV infection and undetectable HBV DNA, both PAT or close monitoring are reasonable options. HBV monitoring should be performed in patients with chronic and past HBV infection, as well as patients with isolated positive HBsAb not acquired by vaccination.

In these studies, together with known case reports, a total of 34 patients (28 with past HBV infection, 4 with chronic HBV infection, and 2 with unknown status) developed HBV-R after receiving novel anticancer drugs, including 11 cases on BTKi,[10–15,29,30] 9 on CAR-T therapy,[9,16–18,26,27,32] 8 on anti-CD38 antibody,[20,21,33] 2 on anti-CCR4 antibody,[23,24] 2 on anti-CD52 antibody,[22] 1 on anti-CD30 antibody–drug conjugate,[19] and 1 on JAK1 inhibitor (the present study). Of these patients, 30 (88.2%) had not received or discontinued PAT prior to HBV-R, again indicating that most reactivations are preventable. Only 4 (1.8%) patients developed HBV-R after continuous PAT with entecavir (3 receiving CAR-T therapy and 1 receiving anti-CCR4 therapy). Two of them died and the other two were managed with entecavir plus tenofovir, suggesting that the combination of entecavir and tenofovir could be used in patients with acquired resistance to prophylactic entecavir treatment. Additionally, 4 patients with chronic HBV infection developed HBV-R, all received CAR-T therapy, and 2 died due to HBV-R. In total, 7 (7/34, 20.6%) patients died of HBV-R. Among them, 4 had past HBV infection and 3 had chronic HBV infection. The median time from HBV-R to death was only 3 weeks, emphasizing the importance of HBV-R prevention. Table 4 shows the detailed information of these 7 patients.

Unexpectedly, HBV-R was observed in 3 of 279 (1.1%, 95% CI: 0.3–3.1) patients with isolated positive HBsAg in this study. To our knowledge, this is the first report of HBV-R in isolated HBsAb-positive patients receiving anticancer drug therapy. HBsAb has been thought to be protective against HBV-R,[34] and patients with isolated positive HBsAb are not considered to be at risk for HBV-R. However, it should be noted that HBsAb titers will decline with time and may lose protective power. In a previous study in lymphoma patients receiving anti-CD20 antibody treatment, the authors found that a considerable proportion of patients with pre-treatment HBsAb titers <100 IU/L lost their HBsAb after treatment, while none of those with pre-treatment HBsAb titers >100 IU/L became negative for HBsAb after treatment. This study indicates that the protective power of HBsAb titers below 100 IU/L is inadequate in lymphoma

Table 4 Detailed information of 7 patients who died of HBV-R in the literature.

Cancer and reference	Age (year)	Novel anticancer drug	HBV infection status at baseline	PAT	Time from initiation of anticancer drug to HBV-R	Antiviral treatment after HBV-R	Time from HBV-R to death	Cause of death
DLBCL[26]	70	CAR-T	Chronic infection with undetectable HBV DNA	Entecavir	4 months	Not clearly reported	Not clearly reported	Septic shock and severe hepatitis
B-cell malignancy[27]	NA	CAR-T and allo-HSCT	Past infection	Entecavir[a]	6 months	Entecavir plus tenofovir	25 days	Hepatitis flare
MM[33]	69	Anti-CD38 antibody	Past infection	No	2 cycles of treatment	Tenofovir	17 days	Hepatic failure
DLBCL[17]	64	CAR-T	Chronic infection with undetectable HBV DNA	No[b]	2.5 months	Entecavir	40 days	Hepatic failure
ATLL[23]	72	Anti-CCR4 antibody	Chronic infection with elevated HBV DNA	Entecavir	4 weeks	Entecavir	3 weeks	Hepatic failure
MM[21]	NA	Anti-CD38 antibody	Past infection	NA	NA	NA	NA	Hepatic failure
CLL[15]	NA	BTK inhibitor	Past infection	No	10 months	Entecavir	6 days	Hepatic failure

[a] Entecavir was discontinued 4.5 months after CAR-T infusion.
[b] Entecavir was discontinued one month after CAR-T therapy.
PAT, prophylactic antiviral treatment; HBV-R, HBV reactivation; DLBCL, diffuse large B-cell lymphoma; CAR-T, chimeric antigen receptor T-cell; NA, not available; allo-HSCT, allogenous hematopoietic stem cell transplantation; ATLL, adult T-cell leukemia-lymphoma; MM, multiple myeloma; CLL, chronic lymphocytic leukemia.

patients receiving immunosuppressive anticancer drugs.[35] This might be the reason of HBV-R in 3 patients with isolated positive HBsAb in the present study. It was a pity that these patients had only pre-treatment S/CO values rather than titers for HBsAb (Supplementary file 1). Another possibility was that these 3 patients were actually past HBV infected-cases, while their HBcAb was false negative due to laboratory errors at baseline. In addition, it is also worth noting that HBcAb reappeared in 19 (6.8%) patients with isolated positive HBsAb. There might be three possibilities for this phenomenon: 1) 12/19 patients received blood transfusion during their treatment. The HBcAb may come from blood doners, as the blood donation screening excluded persons with positive HBsAg rather than positive HBcAb. 2) False negative HBcAb (at baseline) or false positive HBcAb (at the time of conversion) existed due to laboratory errors or values close to cut-off. 3) HBsAb titers declined and lost protective power during anticancer treatment, then patients exposed to HBV and generated HBcAb. More data are needed to get a better understanding of above-mentioned phenomena. In any case, a certain amount of attention should be paid to patients with isolated positive HBsAb receiving immunosuppressive anticancer drugs.

A considerable proportion of the patients in this study were heavily pretreated DLBCL patients or participants in early-stage clinical trials. Their disease conditions generally had a short or no response to the novel drugs, resulting in relatively short exposure time. Therefore, the incidence of HBV-R might be underestimated. Given the limitation of this study, more data are needed to better evaluate HBV-R risk in this population.

Conclusion

Although limited data existed, low incidences of HBV-R and HBV-R-related death were indeed observed in patients with hematological malignancies receiving novel anticancer drugs, especially in patients with PAT. Moreover, the majority of HBV-R episodes were preventable, and the majority of cases experiencing HBV-R were manageable. Based on this, we recommend that novel anticancer drugs should not be intentionally avoided in the management of HBV-infected patients regardless of infection status and HBV DNA levels, as long as liver function is normal. Meanwhile, we emphasize the importance of PAT and HBV monitoring in patients at risk of HBV-R. Moreover, HBV monitoring also has value in patients with isolated positive HBsAb.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.04.003.