Brief Communication

Reactivation of Hepatitis B Virus Among Patients With Cancer Receiving Immunotherapy

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BACKGROUND

Patients with cancer and chronic or past hepatitis B virus (HBV) infection who are receiving anticancer therapy, are at risk for reactivation of HBV and adverse liver outcomes such as hepatitis flare, liver failure, and even death.[1,2] HBV reactivation is defined as increase in HBV DNA or seroreversion of HBV surface antigen (HBsAg) (i.e., change from negative HBsAg to positive HBsAg; Box 1).[2] It is well established that stem cell transplant and anti-CD20 monoclonal antibodies are associated with substantial risk of HBV reactivation. However, the risk of HBV reactivation from immune checkpoint inhibitors (ICIs) is not as well understood, mainly because of lack of data.

With the emergence of ICIs, such as antibodies targeting cytotoxic T lymphocyte antigen 4, programmed cell death 1 (PD-1), and programmed cell death 1 ligand 1 (PD-L1), as an effective therapy for various cancer types, it is important to understand the risk of HBV reactivation from ICIs. However, data about HBV reactivation to guide oncology teams administering ICIs are limited. The purpose of this brief report is to highlight key studies that describe the risk of HBV reactivation in patients receiving ICIs and offer clinical recommendations.

KEY CLINICAL STUDIES

Previous clinical trials of ICIs excluded patients with HBV infection[3]; thus, results from these trials cannot guide HBV management. Mouse models suggested that PD-1 blockade could lead to clearance of HBV infection.[4] However, ex vivo studies showed that PD-1 blockade could lead to hepatitis flare.[5]

We performed a comprehensive literature search in Ovid Medline, PubMed, and Embase to identify clinical studies of HBV reactivation in cancer patients receiving ICIs. We used a combination of controlled vocabulary and keywords including *immunotherapy*, *programmed cell death*, *cytotoxic T lymphocyte antigen*, *monoclonal antibodies*, *hepatitis B*, *virus reactivation*, and *cancer*. Variations on these terms were also included. We found that most of the clinical studies of HBV reactivation in patients with cancer who were receiving ICIs were case reports or small studies. Key clinical studies are summarized in Table 1.

In general, reports of patients with chronic or past HBV infection who were receiving ICIs have shown few cases of adverse liver outcomes, and none have reported liver failure or liver-related deaths. However, case definitions of reactivation or hepatitis flares have not been uniform, and the follow-up monitoring period after ICI initiation may have been unclear. After HBV reactivation was noted, antiviral treatment led to clinical resolution with normalization of liver enzymes and HBV viral levels.

In one of the larger studies, Zhang et al[6] studied 114 patients who had a solid tumor or hematologic malignancy and chronic HBV infection (positive HBsAg) and received anti–PD-1 or anti–PD-L1 therapy during 2015 through 2018. The overall rate of HBV reactivation (see definitions, Box 1) was reported to be 5% (6/114). However, when the analysis was limited to the subset of patients with undetectable HBV DNA at baseline who were not receiving antiviral prophylaxis prior to ICI initiation, the incidence of HBV reactivation was higher, 20.8% (5/24).[6] HBV reactivation resolved in all five patients after initiation of antiviral therapy; subsequent ICI treatment was delayed for three of these patients.

Table 1.—Key studies of HBV reactivation in patients with cancer receiving ICIs

Study, y	Study Type	Patients	Immunotherapy	Risk of HBV Reactivation	Management and Outcome
Zhang et al,[6] 2019	Retrospective study	114 Patients with HBsAg+ and solid tumor or hematologic malignancy treated during 2015–2018	Camrelizumab Nivolumab Pembrolizumab Toripalimab	AASLD definition of HBV reactivation Overall, 5.3% (6/114) had HBV reactivation Among patients with solid tumors with undetectable baseline HBV DNA and not receiving prophylaxis, 20.8% (5/24) had HBV reactivation	4 Patients received antiviral therapy, 5 patients had resolved HBV reactivation, 3 had delayed immunotherapy
Lake,[10] 2017	Case report	1 Patient with lung cancer with HIV, HBV, and HCV treated in 2013 HBsAg−/anti-HBc+ and undetectable HBV DNA prior to anticancer therapy	Nivolumab	HBsAg seroreversion and HBV DNA >170,000,000 IU/mL	Antiviral therapy resolved reactivation
Akar et al,[11] 2019	Case report	1 Patient with renal cell cancer HBsAg+ after anticancer therapy started	Sunitinib Nivolumab	HBV reactivation; HBV DNA detected but level not stated	Antiviral therapy resolved reactivation
Pandey et al,[12] 2018	Case report	1 Patient with lung cancer HBsAg+ after anticancer therapy started	Pembrolizumab	HBV DNA >170,000,000 IU/mL	Antiviral therapy resolved reactivation
Pertejo-Fernandez et al,[13] 2020	Retrospective case series	16 Patients with lung cancer treated during 2014–2018 2 HBsAg+ and 14 HBsAg−/anti-HBc+	Nivolumab Pembrolizumab Atezolizumab Durvalumab Ipilimumab	No reactivation; follow-up period unclear	2 HBsAg+ patients received antiviral prophylaxis 1 Patient with past HBV also had HCV and was receiving antiviral prophylaxis
Shah et al,[14] 2019	Retrospective case series	15 Patients with solid tumor or hematologic malignancy treated during 2011–2018 8 HBsAg+ and 7 HBsAg−/anti-HBc+	Nivolumab Pembrolizumab Atezolizumab Durvalumab Avelumab Ipilimumab	No reactivation; definition not clear Baseline HBV DNA and prophylaxis in HBsAg+ and HBsAg−/anti-HBc+ groups unclear	—
Scheiner et al,[15,16] 2019	Retrospective case series	8 Patients with HCC and HBV infection (unknown if chronic or past HBV)	Nivolumab	No reactivation; definition not clear	—

A dash indicates no information reported.
AASLD: American Society for the Study of Liver Diseases; anti-HBc: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HIV: human immunodeficiency virus; ICIs: immune checkpoint inhibitors.

CLINICAL IMPLICATIONS

One of the early clinical outcomes of HBV reactivation is hepatitis flare, defined as a rise in alanine aminotransferase level to at least three times the baseline level before anticancer therapy and at least 100 U/L (Box 1). Certainly, other causes of hepatitis flare are more common than HBV reactivation, including immune-related hepatitis, which has been reported to occur in 0.3% to up to 33% of patients receiving ICIs,[7] with higher rates noted in patients receiving more than one ICI.

Importantly, steroid therapy, a key component in the treatment of immune-related hepatitis,[8] has been associated with HBV reactivation.[9] Thus, not only ICIs but also treatment of immune-mediated hepatitis can cause HBV reactivation.

Given the risk of HBV reactivation due to ICIs with or without steroid therapy, the HBV status of patients receiving ICIs should be established prior to the initiation of anticancer therapy. Specifically, screening with HBsAg, hepatitis B core antibody (anti-HBc) immunoglobulin (Ig) G or total Ig but not IgM, and hepatitis B surface antibody (anti-HBs) should be done prior to initiation of anticancer therapy.[1] Patients with chronic HBV infection have positive HBsAg, positive anti-HBc, and negative anti-HBs. Patients with past HBV infection have negative HBsAg, positive anti-HBc, and either positive or negative anti-HBs.

Box 1. Definitions of hepatitis B virus reactivation and hepatitis flare[2]

HBV reactivation in patients with chronic HBV infection:

- ≥2 log (100-fold) increase in HBV DNA compared to baseline, or
- HBV DNA ≥3 log (1000) IU/mL if previously undetectable HBV DNA, or
- HBV DNA ≥4 log (10,000) IU/mL if baseline HBV DNA not available

HBV reactivation in patients with past HBV infection:

- HBsAg seroreversion (HBsAg-negative to HBsAg-positive)
- Detectable HBV DNA

Hepatitis flare:

- ALT increase to ≥3 times the baseline and >100 U/L

ALT: alanine aminotransferase; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus.

The risk of reactivation is likely high among patients with chronic HBV infection.[1,2] Patients with chronic HBV infection should be started on antiviral prophylaxis such as entecavir or tenofovir at the beginning of anticancer therapy and maintained on prophylaxis during treatment and up to 12 months after the cessation of anticancer therapy.[1,2] Patients with past HBV infection should be monitored closely during anticancer therapy.[1,2]

If hepatitis flare occurs in patients receiving ICI therapy, clinical evaluation should be performed to assess for HBV reactivation.

CONCLUSIONS AND FUTURE DIRECTIONS

Patients with cancer and HBV infection who are receiving ICIs are at risk for HBV reactivation. The risk of reactivation is likely high among patients with chronic HBV infection, so we believe these patients should receive antiviral prophylaxis and should have their care comanaged with a clinician experienced in HBV management. All patients with cancer and receiving anticancer therapy should be screened for HBV.

Larger studies are needed to define optimal management strategies for patients with HBV infection, especially those with past HBV infection, receiving ICI therapy. Performing universal HBV screening and systematic, long-term monitoring will be essential to ascertain the risk of HBV reactivation associated with specific ICIs or ICI-based combinations.

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