Hepatitis B Virus Screening and Management for Patients with Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update

Hwang et al.
Introduction

- In 2010, the American Society of Clinical Oncology (ASCO) published a Provisional Clinical Opinion (PCO) on chronic hepatitis B virus (HBV) infection screening in patients receiving anticancer therapy for the treatment of malignant diseases.
- PCOs are updated periodically based on review of recently published data.
- ASCO published an updated PCO on this topic in 2015 that introduced a risk-adaptive clinical algorithm to help clinicians identify and treat patients with HBV infection to reduce their risk of HBV reactivation from anticancer therapy.
- This 2020 PCO update presents a clinically pragmatic approach to HBV screening and management that calls for universal HBV serologic testing of patients at the onset of anticancer therapy.
An ASCO provisional clinical opinion (PCO) offers timely clinical direction to oncologists following publication or presentation of potentially practice-changing data from major studies.

The full ASCO methodology manual can be found at:
www.asco.org/guideline-methodology
Statement of the Clinical Issue

- There has been an historical lack of agreement regarding the approach to HBV serologic testing in individuals with cancer, and, as a result, HBV testing has been suboptimal.

- Recent data have called into question the utility of risk-adaptive models for HBV screening.
  - In a multicenter, prospective cohort study of HBV status among individuals newly diagnosed with cancer, Ramsey et al.\(^1\) found that 21% of patients with chronic HBV had no known risk factors for HBV infection.
  - Hwang et al.\(^2\) conducted a large prospective observational cohort study of 2124 patients with cancer to develop various HBV screening strategies prior to the initiation of systemic anticancer therapy. Authors reported that, regardless of the number of questions, about 90% of patients had at least one of the significant risk variables of HBV infection and thus would have needed serologic testing, making selective screening inefficient and impractical.
The results of these two studies suggest that a universal screening approach, its potential harms (e.g., patient and clinician anxiety about management, financial burden associated with antiviral therapy) notwithstanding, \(^3,^4\) is the most efficient, clinically pragmatic approach to HBV screening in persons anticipating systemic anticancer treatment.

Universal HBV testing could identify all cancer patients at risk for HBV reactivation.

Risk-based screening approaches, by contrast, are difficult to implement—many oncologists may be unfamiliar with the risk factors for HBV infection or lack time to conduct a complete HBV risk assessment—and HBV screening rates are low.\(^5\)
Target Population and Audience

Target Population
Newly diagnosed patients receiving anticancer therapy.

Target Audience
Medical oncologists, hematologists, oncology nurses, oncology pharmacists, and other health care professionals who care for patients with cancer, and patients with cancer.
All patients with cancer anticipating systemic anticancer therapy should be tested for hepatitis B virus (HBV) by three tests—hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), total immunoglobulin (Ig) or IgG, and antibody to hepatitis B surface antigen (anti-HBs) prior to, or at the beginning of, systemic anticancer therapy. Anticancer therapy should not be delayed for the results of these screening tests. Findings of chronic HBV (HBsAg-positive) or past HBV (HBsAg-negative and anti-HBc-positive with either negative or positive anti-HBs) infection require further action.

(Type: evidence-based; benefits outweigh harms; Strength of recommendation: strong)
ASCO’s Provisional Clinical Opinion

- Patients with chronic HBV receiving any systemic anticancer therapy should receive antiviral prophylactic therapy for the duration of anticancer therapy, as well as for at least 12 months after receipt of the last anticancer therapy. Monitoring recommendations include checking ALT and HBV DNA level at baseline prior to or at the beginning of their anticancer therapy, as well as every 6 months during antiviral therapy. Hepatitis flares, presenting as elevated alanine aminotransferase (ALT) levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter. Coordination of care with a clinician experienced in HBV management is highly recommended for chronic HBV patients, especially to monitor for withdrawal flares, determine monitoring and antiviral therapy after the cessation of anticancer therapy, and to evaluate for advanced liver disease such as cirrhosis or liver cancer.

(Type: informal consensus; benefits outweigh harms; Strength of recommendation: strong)
Hormonal therapy without systemic anticancer therapy is unlikely to increase the risk of HBV reactivation in patients with chronic or past HBV. Antiviral therapy and management for these patients should follow national HBV guidelines, independent of cancer therapy, including management by a clinician experienced in HBV management for prevention of liver disease such as cirrhosis or liver cancer. Should their anticancer treatment regimen change beyond hormonal therapy alone, the risk of HBV reactivation based on their new anticancer therapy should be reassessed.

(Type: informal consensus; benefits outweigh harms; Strength of recommendation: moderate)
ASCO’s Provisional Clinical Opinion

- Patients with past HBV receiving anticancer therapies associated with an established high risk of HBV reactivation, such as anti-CD20 monoclonal antibodies or stem cell transplantation, should be started on antiviral prophylaxis at the beginning of anticancer therapy and continued on antiviral therapy for at least 12 months after the cessation of anticancer therapy. HBV DNA should be obtained at baseline and followed every 6 months during antiviral therapy. Patients with a negative anti-HBs may be at higher risk of HBV reactivation than patients who have a positive anti-HBs. An alternative pathway is careful monitoring with HBsAg and HBV DNA every 3 months with immediate antiviral therapy at the earliest sign of HBV reactivation (appearance of HBsAg or HBV DNA >1000 IU/mL) so long as patients and providers are able to adhere to frequent and consistent follow up during anticancer therapy and for up to 12 months after last anticancer therapy (as delayed HBV reactivation may occur years after cessation of anticancer therapy). If HBV DNA that is quantifiable but < 1000 IU/mL, then repeat testing at monthly intervals may be indicated. Hepatitis flares, presenting as elevated ALT levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter.

(Type: informal consensus; benefits outweigh harms; Strength of recommendation: strong)
ASCO’s Provisional Clinical Opinion

- Patients with past HBV undergoing anticancer therapies that are not clearly associated with a high risk of HBV reactivation (e.g., regimens that do not include anti-CD20 monoclonal antibodies or stem cell transplantation) should be followed carefully during cancer treatment, with HBsAg and ALT testing every 3 months (with subsequent HBV DNA testing if a hepatitis flare develops) with initiation of antiviral therapy only if HBsAg becomes positive or HBV DNA exceeds 1000 IU/mL in the setting of a hepatitis flare. Follow-up testing after the cessation of anticancer therapy is likely not necessary.

(Type: informal consensus; benefits outweigh harms; Strength of recommendation: strong)
Clinical Considerations: Uniformity of Definitions

- The definition of HBV reactivation has been inconsistent, which has contributed to imprecise estimates of risk and incidence of reactivation. The Expert Panel supports the AASLD definition of HBV reactivation and adverse clinical liver-associated outcomes.\(^6\)

- This PCO uses a simplified cut-off threshold of HBV DNA >1000 IU/mL to assist and guide oncology providers with respect to the threshold above which further management is warranted in patients with past HBV infection. Asymptomatic rises in HBV DNA are very different from clinical hepatitis flares and thus should be interpreted with caution depending on the definitions used.

- Chronic HBV Infection
  - Refers to patients who are HBsAg-positive regardless of anti-HBc status, although most will be anti-HBc-positive.

- Past HBV infection
  - Refers to patients who have a negative HBsAg with positive anti-HBc, regardless of anti-HBs status; HBV DNA is usually undetectable. Among patients with past HBV, if the anti-HBs is positive, then this is considered resolved HBV infection; if the anti-HBs is negative, then this is considered isolated anti-HBc-positive.
Clinical Considerations: Universal HBV Screening

- Large, prospective cohort studies\(^1,2,7\) provide strong, albeit indirect, evidence that supports universal HBV screening in patients with cancer.

- In view of these recent studies, the Panel recommends HBsAg and anti-HBc testing in all patients with cancer prior to systemic anticancer therapy to determine HBV status and appropriate HBV management in order to prevent HBV reactivation.

- The Panel further recommends anti-HBs be performed as part of the screening panel.

- The interpretation of HBV test results may be complicated in patients who have received IVIG known to produce passive transfer of anti-HBc, leading to false-positive anti-HBc test results
Clinical Considerations: Implementation of Universal HBV Screening

- Systems-based approaches have been used to address barriers to the implementation of universal HBV screening in primary care populations.
- Most published efforts utilize electronic health records (EHR).
- HBV screening and linkage to care has also been demonstrated using the EHR in the cancer population.
- In one study, investigators found that HBV screening prior to anti-CD20 therapy increased national rates of HBV testing and antiviral prophylaxis among patients in the Veterans Health Administration receiving anti-CD20 therapy.  
  
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- In another study of patients who received systemic anticancer therapy and were not previously screened for HBV, a computer assisted system was used to send reminders to oncology providers. HBV screening increased from a baseline of 8% to an overall rate of 86%, without significant differences according to cancer type. However, the overall antiviral prophylactic rate was only 46%.  

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Clinical Considerations: HBV Management

- Chronic HBV Infection Management
  - Chronic HBV infection, as part of its natural course, may lead to cirrhosis, liver failure, and/or hepatocellular carcinoma. The risks vary according to patient factors, viral factors, as well as environmental factors.\(^\text{10}\)

  - Patients with chronic HBV receiving any systemic anticancer therapy should be started on antiviral prophylaxis for the duration of anticancer therapy, as well for at least 12 months after receipt of the last anticancer therapy, and they should have a baseline HBV DNA prior to or at the beginning of their anticancer therapy, as well as every 6 months during antiviral therapy.

- Past HBV Infection management
  - Patients with past HBV with hematologic malignancies anticipating anti-CD20 or stem cell transplantation have a high risk of HBV reactivation. These patients should start antiviral prophylaxis prior to anticancer therapy and continue it at least 12 months after the end of anticancer therapy, and even longer as their cumulative risk of reactivation increases until nearly two years after the cessation of anticancer therapy.
Clinical Considerations: Risk Factors for HBV Reactivation

- HBV reactivation has been well-characterized among HBV patients with a hematologic malignancy
  - Risk of reactivation estimated 48% for chronic HBV; 18% for past HBV
- HBV reactivation has been studied less frequently among HBV patients with a solid tumor
  - Risk of reactivation estimated as approximately 25% for chronic HBV; 3% for past HBV
- Of concern is the recent signal of potential complications from HBV after checkpoint blockade immunotherapy
- The risk of reactivation among HBsAg-positive HCC patients has been reported to be 6% after radiation therapy and 20% after radiation therapy and TACE in one large retrospective study of 133 patients
- The reactivation risk identified from rituximab has been extended to other anti-CD20 therapies including obinutuzumab and ofatumumab. Other agents such as blinatumomab and inotuzumab producing B-cell aplasia are anticipated to have high HBV reactivation risks; however, studies of these agents have excluded patients with HBV.
Patient and Clinician Communication

- Patients should be informed of their HBV testing results.
  - Patients who are found to have chronic HBV infection should be referred to and managed in collaboration with a clinician experienced in HBV management to receive ongoing care for their HBV. Patients with a positive HBsAg test should be counseled that they are potentially infectious to others through bloodborne, perinatal, and sexual transmission as well as through close household contact.\(^5,\text{13}\) Screening and vaccination of partners and household contacts is recommended.
  - Patients who have isolated anti-HBc may need further workup because the HBV management for these patients depends on the type of anticancer therapy. These patients are not at risk for transmission through sexually or close personal contact.\(^6\)
  - Patients with a detectable anti-HBs but are negative for HBsAg and anti-HBc can be counseled that they have protective levels of antibody from previous vaccination.
  - Patients who are positive for anti-HBc and anti-HBs have resolved hepatitis B infection and should be counseled that they are at risk, albeit lower than if they had a negative anti-HBs, of HBV reactivation.
  - Patients who are negative for all HBV screening tests are considered not to be immune to HBV, have never exposed to HBV, and may benefit from HBV vaccination.
Cost Considerations

- The consistency of the results from studies estimating the cost-effectiveness of different screening or prophylaxis approaches vary depending on the population studied.

- Universal HBV screening\textsuperscript{14} and antiviral prophylaxis approaches\textsuperscript{15,16} were found to be cost-effective in studies of patients with hematological malignancies at high risk of HBV reactivation.

- Studies of solid tumor patients, by contrast, at lower risk of HBV reactivation due to the treatments received, have been less consistent. Universal HBV screening before the start of anticancer therapy for patients with solid tumors was found to be cost-effective in analyses conducted by Konijeti et al.\textsuperscript{17} and by Wong et al.,\textsuperscript{18} but not cost-effective in analyses conducted by Hwang et al.\textsuperscript{14} and Tan et al.\textsuperscript{19}

- Additional research is needed on HBV screening to address cost-effectiveness more definitively, particularly in patients with solid tumors for whom adequate data on the reactivation risk of commonly used anticancer treatments are lacking.
Additional Resources

More information, including a supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/supportive-care-guidelines

Patient information is available at www.cancer.net
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