Hepatitis B Virus Screening for Patients With Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update
Introduction

• Despite 2010 ASCO’s Provisional Clinical Opinion* (PCO) on chronic hepatitis B virus (HBV) screening in patients receiving cytotoxic chemotherapy, screening is still suboptimal among patients at high risk for HBV infection and HBV reactivation after chemotherapy.

• This updated PCO introduces a risk-adaptive clinical algorithm to help clinicians identify and treat patients with HBV infection to reduce their risk of HBV reactivation from cytotoxic or immunosuppressive therapy.

• Although the evidentiary base remains weak, the Update offers clinically practical approaches based on the best available data.

*Artz et al., JCO, 2010

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PCO Methodology

• An ASCO provisional clinical opinion (PCO) offers timely clinical direction to oncologists following publication or presentation of potentially practice-changing data from major studies.

• ASCO PCOs are updated by an ad hoc panel on the basis of periodic review and analysis of new, potentially practice-changing information on the topic. The members of the PCO panel on HBV screening are listed at the end of these slides.

• The full ASCO PCO methodology supplement can be found at: www.asco.org/pco/hepb
Statement of the Clinical Issue

• In 2013, the US Food and Drug Administration (FDA) revised the product labels of monoclonal antibodies directed against CD20 to include HBV reactivation in the boxed warning.

• Because of the risk of fulminant hepatitis, hepatic flares, and death from HBV reactivation caused by anti-CD20 monoclonal antibodies, the FDA recommends HBV screening for all patients prior to initiation of therapy.
Statement of the Clinical Issue

• Despite 2010 PCO, there is still evidence of suboptimal rates of HBV screening in patient groups at high risk for HBV infection or HBV reactivation after chemotherapy.

• According to ASCO Quality Oncology Practice Initiative, rates of HBV screening among patients with non-Hodgkin lymphoma prior to the initiation of rituximab are approximately 70%.
  – Thus, there may be a substantial group of patients with cancer receiving anti-CD20 monoclonal antibodies who may not have been screened for HBV infection.
ASCO’s Updated PCO

Who should be screened?

• Medical providers should screen by testing patients for HBV infection before starting anti-CD20 therapy or hematopoietic cell transplantation.
• Providers should also screen patients with risk factors for HBV infection.
• For patients who neither have HBV risk factors nor are anticipating cancer therapy associated with a high risk of reactivation, current evidence does not support HBV screening before initiating cancer therapy.

What screening tests should be used?

• Both hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) tests because reactivation can occur in patients who are HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive.
• Either total anti-HBc or anti-HBc IgG (not IgM) tests should be used.

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How to manage HBV patients?

• Clinicians should start antiviral therapy for HBsAg-positive/anti-HBc-positive patients prior to or contemporaneous with cancer therapy and monitor HBsAg-negative/anti-HBc-positive patients for reactivation with HBV DNA and ALT levels, promptly starting antivirals if reactivation occurs.

• Clinicians can initiate antivirals for HBsAg-negative/anti-HBc-positive patients anticipating cancer therapies associated with a high risk of reactivation, or they can monitor HBV DNA and ALT levels and initiate on-demand antivirals.

Are there alternative screening strategies?

• Two panel members provided a minority viewpoint: a strategy of universal HBsAg and selective anti-HBc testing.
Absent solid evidence on mechanisms and predictors of HBV reactivation, especially risk caused by various chemotherapeutic and immunologic therapies, the panel outlines several clinical considerations to guide individualized decision making.

- Physicians should screen patients with cancer prior to initiating B-cell–depleting therapies such as rituximab and ofatumumab.
  - The FDA extended the HBV screening recommendation to a new anti-CD20 monoclonal antibody, obinutuzumab, and would be expected to continue the screening recommendation in the boxed warnings of future anti-CD20 therapies approved for treatment of patients with malignant diseases.
- Time to HBV reactivation was variable but occurred up to 12 months after the last dose of anti-CD20 therapy.
- The panel suggests co-management between oncologists and HBV experts to determine appropriate durations of antiviral therapy and to jointly monitor for interactions between anticancer therapies and antiviral therapy.
Clinical Considerations

Management based on HBV screening test results (II)

- **HBsAg and anti-HBc** tests are recommended for screening prior to cancer therapy for selected patients.
- **Anti-HBs-positive** indicates natural or passive immunity to HBV. Limited evidence to support use in management of HBV reactivation.
- Chronic or resolved HBV infections are both denoted by a **positive anti-HBc IgG test**.
- **HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive** patient should subsequently be tested for HBV DNA.
- **HBsAg-positive/anti-HBc-positive** patients are at elevated risk of reactivation after immunosuppressive therapy and should be started on antiviral prophylaxis before or contemporaneous with cancer therapy.

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Clinical Considerations

Management based on HBV screening test results (II)

- **HBsAg-negative/anti-HBc-positive** patients are also at risk (albeit lower) of reactivation due to persistence of replication competent HBV after HBsAg clearance.
  - HBsAg-negative/anti-HBc-positive patients have undetectable serum HBV DNA levels may still be at considerable risk of reactivation if given a high risk therapy.

- **HBsAg-negative/anti-HBc-positive** (isolated positive anti-HBc test) may reflect either occult chronic HBV infection with lower than detectable levels of HBsAg, or it may reflect clinically resolved HBV infection with lower than detectable levels of anti-HBs.
HBV risk-factor screening. National organizations have identified groups at risk of HBV, but few studies have determined whether HBV risk-based screening is effective to prevent HBV reactivation. The panel suggests HBV screening for patients with cancer and HBV risk factors prior to initiating systemic cancer therapy.

Risk Groups for HBV Infection With a Prevalence of ≥ 2% That Should Be Screened

- Persons born in countries and regions with a prevalence of HBV infection ≥ 2%
- US-born persons not vaccinated as infants whose parents were born in regions with a high prevalence of HBV infection (≥ 8%), such as sub-Saharan Africa and southeast and central Asia
- HIV-positive persons
- Injection drug users
- Men who have sex with men
- Household and sexual contacts of persons with HBV infection
Clinical Considerations

HBV screening strategies

*HBV reactivation risk stratification.* The panel recommends HBV screening prior to anti-CD20 monoclonal antibody therapy and hematopoietic cell transplantation.

- It is likely that other potent B-cell–depleting therapies would pose similar risks as anti-CD20 antibody therapy; patients receiving these potent agents be evaluated and managed in a similar fashion as patients receiving anti-CD20 agents.
- The panel acknowledges that other cancer therapies may place patients at risk of HBV reactivation; however, the lack of strong evidence precludes the panel from a more comprehensive recommendation that includes screening patients prior to other therapies including anthracyclines, prolonged corticosteroids, and certain tyrosine kinase inhibitors.
Clinical Considerations

An alternative HBV screening opinion

- The risk of HBV reactivation is highest among patients who are HBsAg-positive, and prophylactic therapy is an effective antiviral treatment. HBsAg testing is widely available, and previous studies have suggested that HBsAg testing is cost-effective in select and even low prevalence populations.
- Thus, universal HBsAg screening for all patients scheduled to receive systemic cancer therapy is a reasonable alternative that, although yet to be rigorously studied, may be easier to implement than risk-based screening.
Clinical Considerations

HBV management strategies

• Patients who screen positive for HBsAg should receive antiviral therapy during and for 6 to 12 months after completion of systemic cancer therapy.

• **Introduction of antiviral therapy should not delay the onset of cancer chemotherapy but should ideally be started before or concomitant with cancer treatment.**

• Although HBV reactivation has been reported, though not systematically studied, in patients with resolved HBV infection, the risk is likely to be low except in patients receiving anti-CD20 therapies or stem-cell transplantation.

• The optimal management strategy for patients with resolved HBV infection remains unclear.
Clinical Considerations

Anti-hepatitis B therapy (I)

- Prophylaxis refers to antiviral therapy started prior to or contemporaneous with systemic cancer therapy.
- On-demand antiviral therapy refers to the initiation of therapy after evidence of HBV reactivation.
- According to NICE HBV guideline, all immunocompromised patients who are known to be HBsAg-positive should start antiviral prophylaxis before systemic therapy and continue it for a minimum for 6 months after stopping therapy, and likely longer than 12 months for patients receiving anti-CD20 monoclonal antibodies.
- All HBsAg-negative/anti-HBc-positive patients anticipated to receive B-cell–depleting agents should be considered for antiviral prophylaxis or monitored closely and start antiviral therapy if HBV reactivation occurs.
- Once antivirals are initiated, they should be continued up to 12 months after cessation of therapy because of the risk of delayed HBV reactivation.
Clinical Considerations

Anti-hepatitis B therapy (II)

• There are several anti-HB medications available for prophylaxis and on-demand therapy: lamivudine, entecavir, adefovir, tenofovir, and telbivudine.
• Prophylaxis was found to be more effective than on-demand therapy in preventing HBV reactivation, hepatic failure, and mortality.
• Entecavir was found to be more effective than lamivudine, which has higher rates of viral resistance, thus limiting its use, especially for patients requiring long durations of systemic cancer therapies; but entecavir is more expensive than lamivudine.
Research Priorities

• The ad hoc panel emphasizes the need for future collaborative research to better understand the mechanisms and predictors of HBV reactivation.

• Additional research is needed to investigate and identify the HBV reactivation risk by individual cancer therapeutic agents or regimens and among patients with solid tumors.

• Stronger data along with validated risk tools are needed to determine optimal screening strategies before initiating systemic cancer therapies.
Research Priorities

• Research is needed to identify optimal criteria to help clinicians in their decisions to start and stop antiviral prophylaxis.

• Strong data are lacking to determine whether one antiviral therapy is more advantageous than another.

• Overall, the panel recommends collaboration between oncology and hepatitis experts in order to identify key clinical and research areas in order to reduce the incidence of HBV reactivation and to disseminate and implement scientific discoveries.
Additional Resources

More information, including a Data Supplement, Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/pco/hepb

Patient information is available at www.cancer.net
# ASCO PCO Panel Members

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