ASCO Provisional Clinical Opinion: Chronic Hepatitis B Virus Infection in Patients Receiving Cytotoxic Chemotherapy for Treatment of Malignant Diseases

By Robin T. Zon, MD, FACP, and Michael N. Neuss, MD

Michiana Hematology Oncology, South Bend, IN; and Oncology Hematology Care, Cincinnati, OH

In September 2008, the Centers for Disease Control and Prevention (CDC) issued “Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection.”¹ This guideline updates and expands previous CDC recommendations for evaluation and management of chronically hepatitis B virus (HBV) –infected individuals and their contacts to include serologic testing for evidence of hepatitis B infection in all persons receiving any cytotoxic or immunosuppressive therapy. Specifically, it states, “Persons receiving cytotoxic or immunosuppressive therapy (eg, chemotherapy for malignant diseases, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic and gastroenterologic disorders) should be tested for serologic markers of HBV infection (including HBsAg, anti-HBc, and anti-HBs). Prophylactic antiviral therapy can prevent reactivation in HBsAg-positive patients.” These recommendations were based on expert panel consensus around case reports and case series, without comment from the clinical oncology community.

As ASCO members became aware of the CDC recommendations, concerns were articulated regarding the lack of a strong evidentiary base supporting the recommendations. Additional questions were raised concerning the rationale for general population screening rather than screening a defined group of patients from higher risk groups and the possibility of selecting either a more focused or less expensive serologic testing panel. Given that the CDC guideline was recommending a major change in clinical practice with associated costs and risks and potential, but unproven benefits, it was clear that the CDC position required further consideration.

In response to the oncology community concerns, ASCO developed a provisional clinical opinion (PCO) to provide guidance on this issue, which includes a quality assessment of the CDC guideline.² The PCO acknowledges that reactivation of HBV may occur in chronic viral carriers who receive certain cytotoxic or immunosuppressive therapy, including hematopoietic cell transplantation or rituximab-containing regimens in patients with lymphoma. However, the net benefits and harms of general population screening for chronic HBV cannot be estimated, because there is insufficient evidence of the precise risks of HBV reactivation across various malignancies and specific treatment regimens. Notably, the PCO is directed to oncologists practicing in the United States. The PCO recommends that HBV screening follow clinical judgment based on the estimated risk of an individual being a carrier and the degree

of planned immunosuppressive therapy (including hematopoietic cell transplantation and rituximab-containing regimens).

Furthermore, screening tests should include testing for hepatitis B surface antigen and, in some populations, anti-hepatitis B core antigen. When evidence for chronic HBV infection is found, the treating clinician may consider antiviral therapy before and throughout the course of therapy, although evidence from controlled trials of this approach is extremely limited and provides no reliable information on the impact of screening on either liver failure or mortality. Additionally, the PCO does not provide guidance to practitioners regarding specific antiviral agents to utilize, given that there are currently no randomized clinical trials that have compared different antiviral agents in individuals with cancer to inform the discussion. Consultation with an expert may be considered to facilitate optimal antiviral regimen selection for chronic HBV infection in individuals with cancer about to receive immunosuppressive therapy.

Since the publication of the CDC recommendations in 2008, the full effect on the spectrum of oncology practices remains unknown. Some practice communities mandate adoption of the recommendation in toto, whereas other physician practices continue to leave the decision to screen for chronic HBV up to the clinician’s judgment. From a guideline perspective, the widely utilized National Comprehensive Cancer Network guidelines addresses HBV testing in the Non-Hodgkin’s Lymphoma section, citing rituximab and the known association with reactivation of hepatitis B.³ In relation to clinical trials, the amendments from government-sponsored and pharmaceutical studies do not cite the CDC recommendations for HBV screening in the general cancer population. Clinical trials utilizing rituximab-containing therapies routinely require HBV testing. Lastly, the integration of the CDC recommendations into policy by insurers has been inconsistent, with occasional reports of insurers inquiring whether HBV screening is being ordered for individuals undergoing outpatient chemotherapy. HBV testing ordered for patients undergoing hematopoietic cell transplantation and rituximab-containing regimens is reportedly being covered by payers.

However, the impact of the CDC recommendations may not yet be fully realized; it is not clear whether the entire oncology community is familiar with the CDC guideline. The PCO may be of value in raising awareness regarding the issue of potential reactivation of hepatitis B infection in patients belonging to groups at heightened risk for chronic HBV infection and who will be exposed to highly immunosuppressive therapy,

such as hematopoietic cell transplantation or rituximab-containing regimens. Issues such as cost of testing and reimbursement for general screening are not completely transparent.

A key message evolving from the CDC recommendation and the PCO is the need for clinician awareness of chronic HBV infection in individuals with cancer and the potential risk of HBV reactivation and the attendant complications as a result of immunosuppressive treatments. The PCO, in contrast to the CDC guideline, advocates for physician judgment when considering screening, especially for individuals at high risk for chronic HBV infection or if highly immunosuppressive therapies are contemplated. Although an estimated 0.3% to 0.5% of United States residents are chronically infected with HBV and 47% to 70% of these individuals are born outside this country, it is important to acknowledge that there may be large pockets of at-risk groups in different areas of the country.² Clinicians should consider area demographics in their assessments for HBV screening.

The field of oncology is striving to personalize cancer care by targeting interventions along the full spectrum of prevention, diagnosis, treatment, and palliative care. This same approach could potentially be applied, as existing evidence permits, to profile and screen for conditions that are associated with increased morbidity and mortality resulting from oncologic therapies and interventions. The challenges of chronic HBV infection management in patients with cancer represent an opportunity to define the natural history of the disease, including reactivation rates and HBV-related complications, and to better characterize the potential role of antiviral drug therapy in this population. Understanding the benefits and harms of screening for HBV status and the effect of antiviral therapy in combination with chemotherapy in patients with cancer known to harbor chronic HBV infection would assist the clinician in optimizing personalized care for these individuals.

References

1. Weinbaum CM, Williams I, Mast EE, et al: Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep* 57:1-20, 2008
2. Artz SA, Somerfield MR, Feld JJ, et al: American Society of Clinical Oncology provisional clinical opinion: Chronic hepatitis B virus infection screening in patients

Additional Resources

ASCO PCOs alert oncologists to emerging information from recent clinical trials that can assist them in treatment selection. To read the "American Society of Clinical Oncology Provisional Clinical Opinion: Chronic Hepatitis B Virus Infection Screening in Patients Receiving Cytotoxic Chemotherapy for Treatment of Malignant Diseases"² in its entirety, visit <http://jco.ascopubs.org/cgi/reprint/JCO.2010.30.0673v1>.

Authors

The PCO published in *Journal of Clinical Oncology* was developed and written by Andrew S. Artz, Mark R. Somerfield, Jordan J. Feld, Andrew F. Giusti, Barnett S. Kramer, Anita L. Sabichi, Robin T. Zon, and Sandra L. Wong.

Accepted for publication on May 19, 2010.

Acknowledgment

We thank Mark R. Somerfield for his assistance with this article.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Author Contributions

Conception and design: Robin T. Zon

Manuscript writing: Robin T. Zon, Michael N. Neuss

Final approval of manuscript: Robin T. Zon, Michael N. Neuss

Corresponding author: Robin T. Zon, MD, FACP, 100 Navarre Place, Ste 5550, South Bend, IN 46601; e-mail: docrzon@aol.com.

DOI: 10.1200/JOP.777007

receiving cytotoxic chemotherapy for treatment of malignant diseases. *J Clin Oncol* [epub ahead of print on June 1, 2010]

3. Zelenetz AD, Abramson JS, Advani RH, et al: NCCN clinical practice guidelines in oncology: Non-Hodgkin's lymphomas. *J Natl Compr Cancer Netw* 8:288-334, 2010