Hepatitis B Reactivation in Cancer Patients: Role of Prechemotherapy Screening and Antiviral Prophylaxis

Hameem I. Kawsar, MD, PhD, Jamila Shahnewaz, MD, K.V. Gopalakrishna, MD, Timothy P. Spiro, MD, and Hamed A. Daw, MD

Abstract: Hepatitis B virus (HBV) infection is a potentially life-threatening condition that can be effectively prevented by vaccination. In the United States, more than 1.5 million people are infected with HBV, and that number continues to rise with the arrival of immigrants from HBV-endemic countries. Cancer is the second leading cause of death in the United States; 1 in 2 men and women will be diagnosed during their lifetime, and a large proportion of them will require chemotherapy. Chemotherapy-induced immunosuppression can result in HBV reactivation in asymptomatic HBV carriers or patients with resolved HBV infection, causing severe morbidity and mortality. The rate of HBV reactivation depends on several factors, including host and viral factors, and varies from 3–88%. Mortality rates in HBV reactivation range from 23–71%. However, a recent US survey showed that 20% of practicing oncologists never perform any type of HBV screening before the initiation of chemotherapy, and less than 40% perform HBV screening in patients who have high-risk factors for HBV or a history of hepatitis. Given the magnitude of this clinical problem, it is very important to increase awareness among physicians regarding this potentially life-threatening complication. In this article, we review the current understanding of the problem, discuss the existing guidelines from professional societies, and outline a management plan.

Introduction

Hepatitis B virus (HBV) is a small DNA virus that can cause a potentially life-threatening liver infection; it can be effectively prevented by vaccine. HBV has infected approximately 2 billion people worldwide, and 350–400 million people live with chronic infection. An estimated 600,000 people die each year due to the acute or chronic consequences of HBV infection. The prevalence of HBV infection is less than 1% in the United States, and as high as 15% in populations from endemic countries. In the mid-1990s, approximately 1.5 million people in the United States were hepatitis B carriers.
B surface antigen (HbsAg)-positive, and that number continues to rise with the arrival of immigrants from areas of high endemicity.6

The HBV carrier phase is characterized by persistent HBV infection without ongoing inflammation of hepatocytes, negative hepatitis B E antigen (HBeAg), and positive anti-HBe and HbsAg; carriers have serum HBV DNA less than 2,000 IU/mL, and normal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels.7,8 Chronic hepatitis B includes the following criteria: positivity of HbsAg for more than 6 months, serum HBV DNA greater than 20,000 IU/mL, and persistent or intermittent elevation of AST and/or ALT levels.9 Resolved HBV occurs after previous infection without further virologic, biochemical, or histologic evidence of active virus infection or disease in patients with a known history of acute or chronic HBV, or the presence of hepatitis B core antibody (HbcAb) with or without HbsAb. Patients with resolved HBV are HbsAg-negative, have undetectable (or very low levels by sensitive polymerase chain reaction [PCR]) serum HBV DNA, and normal ALT levels.9

HBV infection can be prevented via immunization, safe sex practices, and occupational safety precaution. Some people infected with HBV are clinically asymptomatic as HBV carriers, whereas many infected individuals will develop chronic hepatitis.10

**Hepatitis B Reactivation**

HBV reactivation is marked by the elevation of serum HBV DNA, abnormal liver function tests (LFTs), and clinical features of hepatitis in patients with previously latent or resolved HBV infection.11 A widely accepted definition of reactivation of HBV has 2 components: clinical or histologic features of hepatitis and hepatitis resulting from reactivation of HBV.12,13 Hepatitis is defined by a 3-fold or more increase in ALT above the upper limit of normal value; reactivation hepatitis is defined by a 10-fold or more increase of HBV DNA level above the baseline, or an absolute increase in the HBV DNA level more than 20,000 IU/mL (10⁶ copies/mL) in the absence of other systemic infection.14 Although reactivation can be a spontaneous process, it is usually caused by immunosuppression or immunodeficiency.15 Clinically, reactivation varies from asymptomatic elevation of serum ALT to acute liver failure and death.11,15

**Incidence and History of Reactivation of HBV in Cancer Patients**

In the United States, cancer is the second leading cause of death. One in 2 men and women born today will be diagnosed with cancer during their lifetime, and a large proportion of them will require chemotherapy.16 Chemotherapeutic agents for the treatment of cancers cause profound immunosuppression. In patients who are asymptomatic HBV carriers, chemotherapy-induced immunosuppression can result in HBV reactivation, causing severe morbidity and mortality.12,17,18 In 1975, Wands and associates first described reactivation of HBV in patients receiving chemotherapy for myeloproliferative and lymphoproliferative disorders.19 In 1982, Hoofnagle and colleagues described 2 cases of HBV reactivation in asymptomatic HBV carriers within 3 months of starting chemotherapy.18 The first prospective study on HBV reactivation was published in 1991, and it included Chinese patients with malignant lymphoma who were receiving chemotherapy.12 Several other studies have confirmed this observation of HBV reactivation following chemotherapy, and the median interval between the initiation of chemotherapy and the onset of reactivation is 4 months (range, 1–9 months).12,20–25 The rate of HBV reactivation ranges from 24–88% in patients with chronic HBV infection who have positive serum HBsAg, and from 3–22% in patients who are HbcAb-positive.15,26,27 The mortality rate in HBV reactivation ranges from 23–71%.15,28

**Risk Factors, Chemotherapeutic Agents, and Diseases Associated With Hepatitis B Reactivation**

Due to the lack of well-designed, large, prospective studies, the risk factors for HBV reactivation have not been clearly identified. Most of the risk factors identified to date are based on case studies of small sample size. Not all patients with latent or resolved hepatitis will develop HBV reactivation after starting chemotherapy. In patients treated with cytotoxic chemotherapy, HBV reactivation usually occurs after the second or third course of chemotherapy.12,17 Different host and viral factors, types of chemotherapeutic agents, duration and severity of immunosuppression, and types of malignancies all contribute to determining reactivation of HBV. HBV reactivation also occurs in patients after hematopoietic stem cell transplantation.29 Patients receiving allogeneic stem cell transplant have a higher rate of HBV reactivation than patients receiving autologous stem cell transplant.27,28 Table 1 summarizes the risk factors associated with reactivation of HBV.

Many chemotherapeutic agents are associated with HBV reactivation, including anthracyclines. Glucocorticoids cause HBV reactivation by increasing viral replication. They bind with glucocorticoid-responsive element (GRE) in the enhancer region of the HBV genome.31 In addition to conventional chemotherapeutic drugs, small molecular agents targeted against specific molecules/receptors are becoming popular in cancer treatment. These agents are also associated with HBV reactivation. Rituximab (Rituxan, Genentech/
Biogen Idec), a chimeric monoclonal antibody against CD20 in B lymphocytes that causes B-cell depletion, is now used in the treatment of different malignancies, either as a single agent or in combination with other chemotherapeutic agents. Rituximab is also associated with HBV reactivation. Based on 3 case reports, the US Food and Drug Administration (FDA) issued warnings in 2004 regarding the use of rituximab and risk of HBV reactivation with fulminant hepatitis. In a recent meta-analysis, patients with lymphoproliferative diseases who received rituximab-based therapy had more than a 5-fold higher rate of HBV reactivation than patients who did not receive rituximab. Another small molecular agent, alemtuzumab, a humanized monoclonal antibody against CD52 on lymphocytes, also causes HBV reactivation. Table 2 summarizes the growing list of chemotherapeutic and immunomodulating agents that cause HBV reactivation.

Chemotherapy-induced immunosuppression is now a well-recognized risk factor for HBV reactivation in patients with both hematologic and solid tumors. The incidence of HBV reactivation increases with the rising prevalence of HBV infection.

**Mechanism and Clinical Course of HBV Reactivation**

HBV reactivates when a patient with latent or chronic HBV infection suffers from immunodeficiency or immunosuppression (due to immunosuppressive chemotherapy, steroids, etc.). Hoofnagle described the reactivation process in 3 phases: increase in HBV replication, appearance of biochemical/histologic evidence of hepatic injury, and recovery. In the first phase, viral replication increases, causing an increase in serum HBV DNA. Previously HBeAg-negative patients become HBeAg-positive, and HBsAg-negative patients become HBsAg-positive, in a process known as “reverse seroconversion” or “seroreversion.” The second phase begins with immune reconstruction, when immunosuppressive therapy is decreased or withdrawn. In this phase, hepatitis and hepatic injury takes place, resulting in elevation of biochemical markers in blood (eg, ALT, bilirubin). Viral replication slowly decreases, and HBV DNA level gradually falls. Elevation of serum ALT usually lags behind the elevation of serum HBV DNA by 2–3 weeks. In the third phase, liver injury resolves, and serum HBV DNA level and ALT return to baseline. In some patients, such as organ transplant recipients, immune reconstruction does not occur because immunosuppression is maintained, and these patients do not recover completely. Some of these patients experience chronic hepatitis, whereas others may develop acute liver failure and/or die without any recovery phase.

When considering a diagnosis of HBV reactivation, some other causes of liver dysfunction should be ruled out. These include drug-induced hepatitis, veno-occlusive diseases, hepatic steatosis, hepatic fibrosis, and nodular regenerative hyperplasia.

**Role of HBV Screening in Cancer Patients**

According to the American Association for the Study of Liver Diseases (AASLD) guidelines, which were updated in 2009, every patient requiring immunosup-
pressive treatment should undergo HBV screening prior to the initiation of therapy. Currently, there are several guidelines from different professional societies, including AASLD, the European Association for the Study of the Liver (EASL), the Asian-Pacific Association for the Study of the Liver (APASL), and the Centers for Disease Control and Prevention (CDC). Both the AASLD and CDC recommend screening every patient undergoing chemotherapy. However, the American Society of Clinical Oncology (ASCO) guidelines do not recommend routine screening and use of prophylactic antiviral drugs, citing insufficient evidence for determining the net benefit. According to AASLD guidelines (Table 3), all cancer patients undergoing chemotherapy should be screened for HBV with HBsAg, anti-HBsAg, and anti-HBc.

### Prevention

Prophylactic antiviral therapy is not necessary for all cancer patients undergoing chemotherapy. AASLD and CDC guidelines recommend that uninfected patients (HBsAg-negative, anti-HBsAg-negative, and anti-HBc-negative) should be immediately immunized with hepatitis B vaccine, and chemotherapy should be initiated without antiviral prophylaxis. In HBsAg-positive patients, a baseline serum HBV DNA and liver function test should be obtained, and prophylactic therapy with an antiviral drug should be initiated before starting chemotherapy, regardless of the HBV DNA level. Patients with resolved HBV infection (HBsAg-negative and anti-HBc-positive) who are at high risk of HBV reactivation (such as those undergoing stem cell transplant or receiving rituximab-based chemotherapy), should receive antiviral prophylaxis before the initiation of chemotherapy. An algorithm for the management of HBV reactivation in cancer patients undergoing chemotherapy is presented in Figure 1.

In regard to the initiation of antiviral drugs in cancer patients undergoing chemotherapy, 2 approaches aimed at preventing HBV reactivation have been performed: early prophylactic antiviral therapy (initiated 1 week before or at the start of chemotherapy) and deferred therapy (antiviral therapy not initiated until serologic evidence of HBV reactivation is found). In one study, 87.5% of patients in the deferred therapy group suffered from HBV, despite treatment with lamivudine after HBV reactivation. In a prospective, randomized, controlled study of HBsAg-positive breast cancer patients, early prophylactic lamivudine therapy significantly reduced the incidence of HBV reactivation compared with patients who received lamivudine after developing HBV reactivation (0% vs 28.6%, respectively). In rare cases, patients receiving early prophylactic antiviral therapy can develop HBV reactivation. In a large, prospective, randomized trial of lamivudine prophylaxis for chemotherapy-induced HBV reactivation in patients with non-Hodgkin lymphoma, although HBV reactivation occurred in the prophylactic group, its incidence and severity were significantly reduced. A recent meta-analysis of 14 studies showed that early prophylactic lamivudine reduced the risk of HBV reactivation and HBV-related hepatitis by more than 79% when compared with patients who received deferred or no antiviral treatment. The estimated risk reduction varies from 79–89%, and the number needed to treat (NNT) with lamivudine to prevent 1 reactivation was calculated at 3. In an analytical study on HBsAg-positive lymphoma patients undergoing chemotherapy that included rituximab, anti-HBV prophylaxis improved survival rates by 2.4%. According to the analysis, only 1 out of 1,000 patients will die from HBV reactivation if antiviral prophylaxis is administered, versus 25 HBV reactivation-related deaths if no antiviral prophylaxis is given. In a mathematical model, the costs and outcomes of early preemptive and deferred antiviral prophylaxis with lamivudine in lymphoma patients undergoing chemotherapy were compared. In that model, the use of preemptive lamivudine was cost-effective. For an extra $1,530 per patient, early prophylaxis was effective in reducing the number of HBV reactivations (48 vs 219), liver-associated deaths (0 vs 20), and cancer-related deaths (39 vs 47). Life was prolonged by 0.876 years in the deferred group versus 0.922 years in the early prophylaxis group. Once HBV reactivation occurs, the mortality

### Table 3. Summary of Recommendations by the American Association for the Study of Liver Diseases (AASLD) for Hepatitis B Reactivation

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Screen every person for hepatitis B undergoing immunosuppressive treatment</td>
</tr>
<tr>
<td>B. Screen for HBsAg, anti-HBs (vaccinate seronegative persons), and anti-HBc</td>
</tr>
<tr>
<td>C. Screen before initiation of chemotherapy</td>
</tr>
<tr>
<td>D. Initiate prophylactic antiviral therapy before starting chemotherapy in HBV carriers regardless of baseline serum HBV DNA level</td>
</tr>
<tr>
<td>E. Choice of antiviral drug for prophylaxis:</td>
</tr>
<tr>
<td>a. Lamivudine if anticipated duration of use is &lt;12 months</td>
</tr>
<tr>
<td>b. Entecavir or tenofovir if anticipated duration of use is &gt;12 months</td>
</tr>
<tr>
<td>F. Duration of antiviral prophylaxis: from beginning of chemotherapy to 6 months after completion of chemotherapy in patients with low baseline HBV DNA level (&lt;2,000 IU/mL); if baseline HBV DNA is high (&gt;2,000 IU/mL), continue treatment until reaching treatment endpoints as in immunocompetent patients</td>
</tr>
</tbody>
</table>

HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus.
is high, despite the use of lamivudine. A delay in starting lamivudine allows the virus to replicate and the viral load to become very high, causing severe hepatic injury. Because of the cumulative evidence of benefit, prophylactic use of lamivudine is currently recommended by the AASLD (Table 3), EASL, and APASL guidelines.

**Lamivudine as the First-Line Antiviral Drug**

Lamivudine is the most frequently used nucleoside analog for the treatment of HBV reactivation. It prevents the incorporation of the natural nucleoside analog into HBV DNA. Lamivudine acts as a competitive inhibitor of the viral reverse transcriptase and DNA polymerase, and exerts minimal effect on restoration of host immunity. It is effective in preventing HBV reactivation in patients undergoing chemotherapy for hematologic or nonhematologic malignancies. AASLD guidelines recommend continuing lamivudine treatment for 6 months after the completion of chemotherapy. A prolonged treatment with lamivudine may be necessary in patients who receive monoclonal antibodies or have high baseline HBV DNA. Late reactivation of HBV due to premature termination of lamivudine treatment has been reported. Therefore, patients should be routinely followed after discontinuation of preventive lamivudine therapy, with serial serum ALT and HBV DNA levels measured every 1–3 months for the
first 6 months, and every 3–6 months thereafter. Lamivudine should be reinstated if there is an increase in serum HBV DNA level from baseline. Long-term treatment options should be considered in patients with persistent elevation of serum ALT and detectable serum HBV DNA.

Prolonged use of lamivudine is associated with an increased emergence of lamivudine-resistant HBV variants, with the substitution of methionine in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV DNA polymerase for valine or isoleucine. The rate of resistance increases with prolonged use of lamivudine (from 14–32% at 1 year to 60–70% after 5 years). Factors associated with an increased rate of resistance include prolonged use of lamivudine, a high baseline serum HBV DNA, and a high level of residual virus after treatment initiation. In some cases, resistant strains have emerged after 6–8 months of prophylactic lamivudine use. The emergence of resistance is marked with abrupt elevation of serum ALT and HBV DNA levels. Careful monitoring for HBV reactivation with serum ALT and HBV DNA is necessary when the patient is being treated with prophylactic lamivudine. In patients with decompensated cirrhosis, lamivudine therapy can cause flares resulting in liver failure and death. Withdrawal flares have been also reported after cessation of lamivudine. Up to 13% of patients have developed flares within 3 months of lamivudine withdrawal. This withdrawal flare is associated with high baseline serum HBV DNA.

Newer Antiviral Drugs and Their Use in HBV Reactivation

New nucleoside analogs, such as adefovir (Hepsera, Gilead), entecavir (Baraclude, Bristol-Myers Squibb), telbivudine (Tyzeka, Novartis), and tenofovir (Viread, Gilead) are now approved for the treatment of HBV infection and are more potent than lamivudine. Both adefovir and entecavir are active against lamivudine-resistant HBV. In a prospective study, adefovir was successfully used as a salvage treatment in lamivudine-resistant or lamivudine-relapsed patients with hematologic malignancies who were undergoing chemotherapy. Resistance associated with telbivudine is relatively high, and both telbivudine and entecavir have decreased efficacy against lamivudine- and adefovir-resistant HBV. However, tenofovir is potent in patients who have started a new lamivudine regimen as well as in those who have received treatment previously. The degree of HBV DNA suppression with adefovir is less than that achieved with lamivudine, but the cumulative incidence of resistance is lower than that of lamivudine. Adefovir-resistant HBV is susceptible to lamivudine and entecavir. Although adefovir has the disadvantage of being potentially nephrotoxic, its low rate of resistance makes it a first-line drug when prolonged treatment is necessary. Adefovir is effective when used alone or in combination with lamivudine.

Entecavir is a carbocyclic analog of 2′-deoxyguanosine. It is more potent than lamivudine and adefovir, and it is effective against lamivudine-resistant HBV. In 2 randomized phase III clinical trials, entecavir (compared to lamivudine) showed a higher rate of viral suppression and arrested the progression of liver diseases. In one case study, a patient with non-Hodgkin lymphoma developed HBV reactivation after treatment with rituximab-containing chemotherapy, and was successfully treated with entecavir and tenofovir. In 2 other case reports, entecavir was used as first-line treatment for HBV reactivation following rituximab-containing polychemotherapy for chronic lymphocytic lymphoma and large B-cell lymphoma. In a retrospective, multicenter, nonrandomized controlled trial, lymphoma patients treated with entecavir (vs patients treated with lamivudine) had significantly lower rates of hepatitis (5.9% vs 27%, respectively), HBV reactivation (0% vs 12.4%, respectively), and interruption of chemotherapy (5.9% vs 20.2%, respectively). In another report, a 62-year-old woman with follicular lymphoma and a 62-year-old man with mantle cell lymphoma (both with prechemotherapy HBsAg-positive and anti-HBc–positive status) were treated with a rituximab-containing polychemotherapy regimen. Both patients were given entecavir prophylactically along with the chemotherapy, and they successfully completed the chemotherapy without HBV reactivation. Entecavir is a potent antiviral drug with a very low rate of virologic breakthrough. Recently, higher risk of genotypic resistance to entecavir has been reported in lamivudine-resistant patients. Thus, entecavir would likely be better as first-line therapy rather than rescue therapy in patients who develop lamivudine resistance.

Telbivudine is a synthetic thymidine nucleoside analog. It is more potent than lamivudine, but is associated with a higher rate of resistance. Therefore, telbivudine is not typically used as monotherapy in the treatment of HBV. Tenofovir disoproxil fumarate is a prodrug of tenofovir, and is structurally similar to adefovir. It is more potent than adefovir at suppressing lamivudine-resistant HBV DNA. Table 4 summarizes the important features of the antiviral drugs currently approved for the treatment of HBV.

Conclusion

HBV carriers with cancer who are undergoing chemotherapy are at higher risk of developing HBV reactivation. The risk is greater in patients with high baseline serum HBV DNA levels, and in patients receiving chemotherapy regimens that contain steroids and rituximab. This is a serious clinical problem that remains a challenge for the practicing oncologist. HBV reactivation often requires withholding chemotherapy, which increases both liver- and cancer-related morbidity and
mortality. Screening for HBV before the initiation of chemotherapy and early antiviral prophylaxis has significantly decreased the morbidity and mortality, and is cost-effective. Although several professional societies, including AASLD, EASL, APASL, and CDC, recommend screening for HBV in every cancer patient undergoing chemotherapy, in the United States, 20% of oncologists never perform any type of HBV screening before the initiation of chemotherapy; additionally, fewer than 40% perform HBV screening in patients with high-risk factors for HBV, or in patients with a history of hepatitis.103 We believe that it is very important to increase awareness of this potentially life-threatening complication among the oncology community.

Despite extensive studies regarding HBV reactivation, there are several areas of uncertainty. Which antiviral agents should be used initially, how long the prophylaxis should be continued, and how long patients should be monitored for viral reactivation after termination of therapy are questions that remain unanswered. To determine whether lamivudine should be the drug of choice, or if newer antiviral agent(s) should be used as first-line therapy, larger, prospective, randomized, controlled studies are required.

Acknowledgment
We would like to thank Dr. Bernard Tandler of Case Western Reserve University for critically reading and editing this article.

References
Clinical Advances in Hematology & Oncology Volume 10, Issue 6 June 2012


