

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Preventing Hepatitis B Viral Reactivation in Patients Receiving Cancer Chemotherapy

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### **G&H** What cancer patients are at the highest risk for hepatitis B viral reactivation during chemotherapeutic treatment?

**AR** Generally, any patient with chronic hepatitis B virus (HBV) infection is at risk for reactivation of the virus following the initiation of cytotoxic chemotherapy. The risk of reactivation increases in patients with greater HBV activity at the start of cancer treatment. Patients undergoing chemotherapy who already had been diagnosed with HBV infection with overtly active virus are usually not at issue because they are, ostensibly, already under anti-HBV treatment and therefore at a lower risk of reactivation. Those who have active disease with replicating HBV who are not on treatment (eg, those who have not yet been diagnosed) are at a high risk of a flare of liver disease. It is therefore important to screen every patient for HBV infection prior to the initiation of chemotherapy.

Among patients with HBV activity low enough to suspend treatment, such as those in an inactive carrier state, there is a need for prophylactic HBV therapy before and during the administration of cancer chemotherapy or immunosuppressive treatment. Patients with more active viral replication based on serology (positive hepatitis B e antigen) or HBV DNA levels are more likely to relapse. However, even patients with the lowest HBV DNA levels and hepatitis B e antigen–negative disease are not free of risk and should receive prophylaxis as well.

### **G&H** Are there specific cancers that impart greater risk of HBV reactivation?

**AR** Patients with lymphoma have been shown to be at a high risk of reactivation, as are patients with breast

cancer. It is probably a combination of the cancers themselves and the aggressive nature of the chemotherapeutic regimens utilized for these cancers that imparts the higher risk. Again, patients who do not have these particular cancers are still at some risk and should be treated prophylactically, even if they are administered lower-risk chemotherapy regimens.

### **G&H** What are the clinical manifestations of chemotherapy-induced HBV reactivation?

**AR** The clinical manifestations range from asymptomatic increase of serum aminotransferase levels to overt acute hepatitis, liver failure, and death. Typically, reactivation occurs after the discontinuation of chemotherapy, with the restoration of the immune system. Severely affected patients may present with jaundice and can rapidly develop ascites and encephalopathy. Liver-related mortality ranges in different reports from 5% to 22%.

### **G&H** What are the specific prophylactic measures that can be administered to cancer patients in order to prevent HBV reactivation?

**AR** Fortunately, the current treatment, even for active HBV infection, is based on oral nucleoside or nucleotide analogs, which are highly effective in suppressing the virus and have very few side effects. These agents can be used as prophylactic treatment, at the standard doses. Of these agents, lamivudine (Epivir, GlaxoSmithKline) is the most actively investigated in this setting, simply because it has been in use the longest. Lamivudine is a highly effective treatment and a good option for prophylaxis, but there

are newer products that are probably just as good, if not better, though they are not as well studied.

We generally use lamivudine in this setting, but adefovir dipivoxil (Hepsera, Gilead), entecavir (Baraclude, Bristol-Myers Squibb), and telbivudine (Tyzeka, Idenix) would likely be effective for the same purpose. However, if the patient has a history of lamivudine therapy and is about to receive chemotherapy, it may be prudent not to rely on lamivudine for prophylaxis because these patients may have developed lamivudine resistance. These patients should usually receive adefovir, which does not overlap with lamivudine in terms of resistance profile.

Prophylactic therapy with interferon is not an option in these patients. Interferon suppresses white blood cell and platelet counts in a manner similar to chemotherapy. It may cause severe side effects, which will be compounded by the already prohibitive side effect profile of chemotherapeutic regimens.

#### **G&H** How long should these patients be treated with prophylactic anti-HBV therapy?

**AR** There are insufficient data regarding the optimal timing of initiation and discontinuation of prophylactic antiviral treatment. We recommend initiating anti-HBV treatment at least 1 week before the beginning of chemotherapy and discontinuing it at least 3–6 months after the resolution of the immunocompromised state. However, anti-HBV treatment should not be stopped if there is biochemical or serologic evidence to suggest HBV reactivation.

#### **G&H** What other supportive measures are required for these patients?

**AR** Prophylactic treatment is only one aspect of the care of these patients. The other part, which is extremely important, is the very close monitoring of HBV serology and viral load as well as hepatic biochemical tests. Although the initial reactivation of the virus may be clinically silent, it can be detected through blood work. It may initially manifest as only an increase in HBV DNA levels. Subsequently, there may be changes in serology and conversion from hepatitis B e antigen negativity to positivity. Only after these changes will there be alanine aminotransferase and aspartate aminotransferase elevations and subsequent clinical signs and symptoms.

Close follow-up is particularly important in patients with some level of liver damage due to chronic HBV infection. These patients face a higher risk of liver failure if they develop reactivation and also require close follow-up and monitoring. If the patient has progressed to cirrhosis, it may require alteration of their chemotherapeutic regimen.

#### **G&H** Can these measures be extended to other disease states in patients with inactive HBV infection?

**AR** Whether the range of these recommendations should be extended to other immunocompromised states is a very serious question. Beyond patients who are receiving classic immunosuppressive treatment, such as chemotherapy for cancer, there are those with other conditions, like asthma, vasculitis, and sarcoidosis, who may receive courses of high-dose steroids or other immunosuppressive medications. There is scarce information regarding the risk of HBV reactivation in these groups, and as a result there are many unanswered questions. Should these patients be tested for HBV infection before the initiation of immunosuppressive treatment? If they are found to have positive serology for hepatitis B, should they receive HBV reactivation prophylaxis? These are issues that need to be examined in a wide variety of disease states. Because we now have oral medications that are safe and effective in suppressing the hepatitis B virus with minimal side effects, prophylaxis is possible in virtually any clinical scenario and should be studied as such.

#### **Suggested Reading**

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