Association of Lymphomagenesis and the Reactivation of Hepatitis B Virus in Non-Hodgkin Lymphoma

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**Background:** Hepatitis B virus (HBV) has been associated with the development of non-Hodgkin lymphoma (NHL) and can be reactivated in patients being treated for NHL.

**Methods:** Articles published between 2000 and 2015 that discussed an association between NHL and HBV, mechanisms of HBV induction of NHL, and HBV reactivation in patients with NHL were reviewed and the results compiled to help health care professionals better understand the risk of developing NHL in HBV-seropositive individuals, describe potential etiologies by which HBV infection may lead to lymphomagenesis, and highlight the recent medical literature with respect to the reactivation of HBV in the setting of NHL.

**Results:** An association exists between HBV infection and NHL development. Immunosuppression due to HBV, chronic viral stimulation, and dysregulation of the immune system are possible ways in which lymphoma can develop in patients with HBV infection. All patients being treated with anti-CD20 antibodies or those from or living in HBV-endemic regions should be tested for hepatitis B surface antigen, core antibody, and surface antibody prior to initiating therapy. HBV DNA polymerase chain reaction (PCR) may also be useful in certain cases. Among HBV-seropositive patients or those with detectable HBV DNA, prophylaxis with an antiviral agent should be initiated for 1 year after NHL therapy. HBV DNA PCR monitoring should be undertaken each month during the course of treatment and every 3 months after treatment for a 1-year duration.

**Conclusions:** Health care professionals should become more comfortable treating these high-risk patients with NHL as they become more informed about potential lymphomagenesis and the reactivation of HBV.
Methods
Articles published between January 2000 and January 2015 were included in our review if they discussed either an association between the development of NHL and HBV infection, mechanisms of HBV induction of NHL, and the reactivation of HBV in patients with NHL. Using these articles, we summarized the current literature with regard to HBV and its association with NHL, possible mechanisms for how HBV may induce NHL, the clinical characteristics of HBV reactivation, and the use of prophylaxis for the prevention of HBV reactivation in at-risk patients with NHL.

Causal Associations
Many epidemiological studies during the last decade have shown mixed results as to whether a causal relationship exists between HBV infection and NHL.12,15-44 Two meta-analyses summarized these epidemiological studies, and their conclusions suggest that an association might exist between HBV infection and the development of NHL.9,14 In a comprehensive meta-analysis of 17 case-control studies and 5 cohort studies, which made up more than 40,000 cases of NHL, HBV-seropositive individuals had an odds ratio of 2.24 (95% confidence interval [CI]: 1.80–2.78) for developing NHL.9 Similarly, Nath et al11 reported an odds ratio of 2.67 (95% CI: 2.04–3.49) for detecting HBV infection in individuals with NHL when compared with controls, suggesting a high prevalence of HBV-carrier states in patients with NHL.

Furthermore, in the meta-analysis by Dalia et al,9 risk was stratified by common NHL subtypes (eg, diffuse large B cell, follicular) and by World Health Organization (WHO) high, intermediate, and low-prevalent HBV countries. In this subanalysis, an increased risk for diffuse large B-cell lymphoma was seen, as well as an overall trend toward increased risk for developing follicular and T-cell lymphomas; this trend was driven by WHO high-prevalent HBV countries.9 These findings suggest that the risk for developing NHL in patients with HBV infection may be more driven by the high prevalence of HBV in HBV-endemic countries. Thus, HBV-endemic countries may be a target population for future research to better understand whether HBV seropositivity leads to an increased risk for developing NHL.

Based on the findings from those 2 meta-analyses,9,14 health care professionals must keep in mind that patients with HBV seropositivity may be at risk for developing NHL, and this is particularly true for patients from or living in high HBV-endemic regions. If patients with HBV infection are symptomatic (eg, B symptoms, lymphadenopathy), then further work-up should be undertaken to rule out NHL; however, NHL screening has no role in patients with HBV seropositivity, and further research is needed to confirm such an epidemiological association.

Mechanisms
The biological mechanisms responsible for the development of NHL are ambiguous and unclear; however, genetics may predispose certain families to NHL.45 Genetic alterations, such as translocations and growth-factor damage, may lead to immunosuppression, cell-growth dysregulation, cell-signaling pathway dysfunction, lack of programmed cell death, and the dysregulation of immune processes. Multiple hypotheses have been suggested to explain the underlying etiology of these changes and alterations, particularly in relation to viral infections that may lead to lymphomagenesis.45-47 Chronic viral infections stimulate the proliferation of B cells, leading to a higher probability of random genetic mistakes and errors — particularly those related to immunoglobulin genes. Irrespective of whether immunosuppressive states are directly related to the viral infection itself or indirectly related by down-regulating the responses of T cells, these immunosuppressive states may lead to the body’s inability to eliminate malignant cells as a consequence of impaired immune surveillance. Such cases have been observed in the context of inherited or acquired immunodeficiency syndromes as well as among patients receiving immunosuppressive therapy.46,47 All of these mechanisms — genetic predisposition, impaired immune surveillance, and chronic viral infection — likely cooperate to influence the development of lymphoma.

Mechanisms that may be specific to HBV-associated NHL have been largely extrapolated from studies evaluating HBV-associated hepatocellular carcinomas and HCV-associated NHL.21,25,29,31,48-55 In particular, HBV-specific nucleic acid sequences in peripheral blood mononuclear cells and hematopoietic tumor cells among patients positive for hepatitis B surface antigen (HBsAg) suggest that HBV may have a direct cellular effect that impacts lymphomagenesis.21,25,29,48 The chronic stimulation of B cells encountered by this mechanism may predispose these patients to increased DNA damage, thus leading to the transformation of B cells into malignant B cells. The immunological response to chronic, local antigenic stimulation has been proposed as a mechanism of HCV-mediated lymphomagenesis and may also be a way in which HBV mediates lymphomagenesis because the 2 viruses are similar in structure.49-53 HBV-encoded X protein has been shown in liver cells to inhibit p53 and lead to the abnormal division of liver cells, thus leading to hepatocellular carcinoma.50,52-55 A similar B-cell mechanism is possible and may contribute to the malignant transformation and development of B-cell NHL.29,30,48,54 Similar to hepatocellular carcinoma, an indirect role of lymphomagenesis may exist via HBV-specific, immune-mediated cell injury and im-
munodeficiency.\textsuperscript{25,51} HBV infection of endothelial cells may also serve as a trigger for the increased production or release of hematopoietic tumor growth factors, stimulating cell proliferation and leading to NHL.\textsuperscript{33} It may also be possible that an unknown virus with a mode of transmission similar to HBV might be cotransmitted with HBV and is responsible for lymphomagenesis, but no such virus has been found to date.\textsuperscript{21,29,56} Thus, additional research is needed to better understand the mechanisms by which HBV seropositivity may lead to the development of NHL.

**Reactivation**

The role of the oncologist in recognizing and communicating the risks of chemotherapy to his or her patients has become complex with the addition of biological agents. These agents have various adverse events that can impact immune function for extended periods of time. Therefore, health care professionals must be aware of the reactivation of HBV among HBV-seropositive patients receiving chemotherapy and anti-CD20 antibodies (eg, rituximab, ofatumumab).\textsuperscript{57-69}

Rituximab-associated HBV reactivation was investigated in a systematic literature review and meta-analysis first published in 2010.\textsuperscript{66} In this study, the authors concluded that 55% of the 183 cases reported in the medical literature experienced liver failure and had an associated mortality rate of 48%.\textsuperscript{66} A fivefold increase in HBV reactivation was also seen in the patients positive for hepatitis B core antibody (HBcAb) who received rituximab-containing treatments compared with those who received chemotherapy alone.\textsuperscript{66} The association between anti-CD20 antibodies and HBV reactivation with subsequent hepatic failure resulted in a black box warning for both rituximab and ofatumumab regarding the risks of HBV reactivation.\textsuperscript{60}

HBV reactivation defines a specific syndrome marked by the rise of HBV DNA in a patient with previously resolved or inactive HBV infection. A common definition of reactivation involves demonstrating 2 distinct components: (1) a threefold increase in serum transaminase level (alanine transaminase $> 3$ times the upper limit of normal), and (2) a tenfold increase in the HBV DNA above baseline or at a level of more than 20,000 IU/mL and clinical evidence of hepatitis.\textsuperscript{70} The clinical spectrum of acute reactivation of chronic hepatitis B can range from subtle elevations in transaminase to frank hepatic failure. Patients who develop HBV reactivation are treated with antiviral therapies, such as lamivudine, and with supportive care; rates of morbidity and mortality continue to be high.

Vega et al\textsuperscript{71} demonstrated that 43% of study patients with positive serology developed liver-related adverse events, defined as an elevated transaminase level more than twice the upper limit of normal, new or progressive cirrhosis, hepatic necrosis, and mortality related to liver failure. In this study, study patients with underlying liver disease appeared to have worse outcomes than those with no baseline liver dysfunction.\textsuperscript{71} The rate of short-term mortality depended on the degree of hepatic necrosis and was not directly dependent on HBV load.\textsuperscript{71}

The exact frequency of spontaneous reactivation remains unclear; however, the results of one study suggest that the annual incidence may be 7.3%.\textsuperscript{72} Typically, reactivation occurs in the setting of immunosuppression or immunodeficiency (eg, patients with NHL).\textsuperscript{70} Reactivation rates in patients treated with cytotoxic chemotherapy or anti-CD20 antibodies who are positive for either HBsAg or HBcAb range from 24% to 88% and 3% to 22%, respectively.\textsuperscript{69,75,74} In the setting of chemotherapy, the mortality rate from HBV reactivation ranges from 23% to 71%.\textsuperscript{75,76} False-negative results for HBsAg can occur in patients with chronic liver disease and, thus, patients with a history of hepatitis in need of chemotherapy or immunotherapy should be assessed by HBV load.\textsuperscript{77}

Because of the morbidity and mortality associated with HBV reactivation, particularly among patients with NHL receiving anti-CD20 antibody therapy, guidelines suggest that testing for both HBsAg and HBcAb should be performed in all patients receiving anti-CD20 antibody therapy.\textsuperscript{58,78} In addition, testing should be performed for all patients receiving any treatment for NHL who are from or live in a highly prevalent HBV region because research indicates that HBV can be reactivated in patients who have received cytotoxic chemotherapy without any prior immunotherapy.\textsuperscript{58,78} Hepatitis B surface antibody (HBsAb) should also be tested in all patients receiving anti-B-cell therapy; among those positive for HBcAb or HBsAb but negative for HBsAg, HBV DNA levels should also be measured.\textsuperscript{79} Of note, patients receiving intravenous immunoglobulin may be positive for HBcAb as a result of that treatment, so HBV DNA levels should also be measured in these patients (Table).\textsuperscript{80} Study results have also suggested that screening for patients with NHL receiving anti-CD20 antibodies was a cost-effective measure, thus providing additional evidence for the screening of all patients for HBV seropositivity receiving treatment for NHL.\textsuperscript{61,81,82}

Because patients with NHL treated with lymphoma-directed therapy are at high risk for HBV reactivation, the National Comprehensive Cancer Center (NCCN) recommends either prophylaxis or active surveillance of patients with NHL undergoing immunosuppressive therapy (chemotherapy or anti-CD20 antibody therapy).\textsuperscript{83} Prophylaxis with antiviral therapy should be provided for patients positive for HBsAg. Among those positive for HBcAb or HBsAb but negative for HBsAg, the HBV DNA load should determine...
whether prophylaxis is required rather than active surveillance.79 For example, if the HBV DNA load is detectable, then prophylaxis is recommended.79 In patients for whom prophylaxis cannot be provided, then close surveillance with quantitative HBV DNA levels can be performed and antiviral therapy can be initiated early in patients with a rising HBV DNA load.74

Studies supporting the use of antiviral prophylaxis include a small, randomized trial of 30 participants with lymphoma and positive for HBsAg who were randomized to either prophylaxis with lamivudine or deferred, preemptive therapy (antiviral therapy was started at the time of serological evidence of HBV).84 Those assigned to preemptive therapy had a reactivation rate of 53%, whereas those assigned to lamivudine had a reactivation rate of 0% during lymphoma-directed therapy.84 Other studies with lamivudine showed similar rates of efficacy.76,85-90 In a meta-analysis, patients positive for HBsAg on lamivudine prophylaxis had a reduced rate of HBV reactivation (risk ratio 0.21; 95% CI: 0.13–0.35) and there was a trend toward reduced HBV-related deaths compared with those who had no prophylaxis.90 It is worth noting that most of these studies of lamivudine followed study patients for serological relapse, not detectable HBV DNA loads, and this may be why salvage antiviral therapy was ineffective in most study participants.

Other antiviral agents, such as entecavir, have been shown to be more effective at preventing HBV reactivation in patients who are HBV seropositive.74,91,92 In a prospective study of 229 study patients with diffuse large B-cell lymphoma treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, those positive for HBsAg were randomized to receive either entecavir or lamivudine.92 Entecavir was associated with lower rates of HBV-related hepatitis (0% vs 13.3%; \( P = .003 \)) and HBV reactivation (6.6% vs 30%; \( P = .001 \)).92 This finding suggests that entecavir may be a more appropriate antiviral agent for prophylaxis than lamivudine,92 although more studies are needed to confirm this result. Other potentially effective antiviral agents include tenofovir or adefovir, although data relating to oncology patients are lacking. The NCCN recommends using entecavir for prophylaxis in HBV-seropositive patients receiving therapy for NHL and monthly surveillance with HBV viral load via polymerase chain reaction during treatment and then every 3 months after treatment for a duration of 1 year (see Table).84

### Conclusions

Health care professionals should be suspicious of hepatitis B virus (HBV) infection in patients who develop non-Hodgkin lymphoma (NHL) and live in or are from HBV-endemic areas. Patients receiving chemotherapy — in particular, anti-CD20 antibodies — should be tested for hepatitis B surface antigen, core antibody, and surface antibody as well as HBV DNA load in certain cases prior to the initiation of therapy. Patients who have HBV seropositivity or a detectable HBV DNA load should be prophylactically treated with antiviral therapy (eg, entecavir) while receiving treatment for NHL; this prophylaxis should continue for 1 year after the therapy for NHL has ended. By clinicians becoming more aware of the possible reactivation of HBV and by understanding the use of antiviral prophylaxis and surveillance, the high rates of morbidity and mortality from HBV reactivation might be avoided. Further research is needed to better understand the lymphomagenesis of HBV to NHL and to find better agents for prophylaxis and treatment options for patients with NHL who develop HBV reactivation.

### References