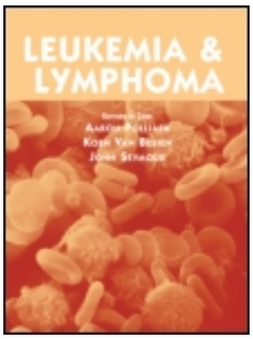

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Hepatitis-B reactivation and rituximab-containing chemotherapy: an increasingly complex clinical challenge

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COMMENTARY

Hepatitis-B reactivation and rituximab-containing chemotherapy: an increasingly complex clinical challenge

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Hepatitis B virus (HBV) infection is a major global health problem, with at least one in three people having been infected, and conservative estimates of current prevalence indicating that at least 350 million people worldwide are living with chronic infection. Seventy-five percent of these are in Southeast Asia and the Western Pacific regions [1].

The role of the immune system in controlling HBV infection is well recognized. Lysis of HBV-infected hepatocytes is predominantly mediated by CD8+ cytotoxic T-cells. However, B-cells may also act as antigen-presenting cells, and prime cytotoxic T-cell specific responses [1]. Reactivation of HBV in association with chemotherapy-related immunosuppression has been documented in multiple settings, including lymphoproliferative and myeloproliferative neoplasms, solid malignancies, and hematopoietic stem cell transplant (HSCT) [1]. Reactivation may occur during or after chemotherapy [1], but the duration of risk is not well defined. However, it persists for at least 6 months after cessation of chemotherapy [2] and is influenced by multiple factors, in particular the pre-treament level of viral replication, as measured by HBV DNA levels [2].

The importance of HBV reactivation is two-fold. First, symptomatic hepatitis flare carries a high mortality rate, which has ranged from 5 to 40% in various reports [3–6]. Second, HBV reactivation, if it occurs prior to completion of chemotherapy, will likely result in substantial delays in the delivery of potentially curative chemotherapy for the underlying malignancy. Given the clear documentation that dose density is strongly correlated with outcome in aggressive non-Hodgkin lymphoma, such delays are detrimental to long-term cancer-specific outcome [7].

Established risk factors for reactivation of HBV include the intensity of immunosuppressive therapy: patients undergoing HSCT have a higher incidence; and patients undergoing lower-intensity treatment, such as for gastrointestinal malignancies, have a lesser risk of reactivation [8]. Duration of chemotherapy has not been shown to be a risk factor [9], although patients having second- and third-line chemotherapy [10] are at higher risk, probably related to the cumulative immunosuppression of sequential therapies. The use of glucocorticoids [8,11,12] and anthracyclines [13] has been reported to increase the risk of reactivation through specific mechanisms. However, the overall degree of immunosuppression is also likely to be important [1]. It is increasingly becoming recognized that rituximab is associated with a heightened risk of HBV reactivation [14–16]. Recently, Yeo *et al.* showed that the addition of rituximab to standard CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) markedly increased the risk of HBV reactivation in patients with 'resolved' HBV infection, defined as surface antigen (HBsAg) negative, core antibody (HBcAb) positive, a group thought

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previously to be at extremely low risk [17]. Virological risk factors for reactivation include the presence of pre-core HBV mutants (HBeAg-negative chronic, replicative infection), high pre-chemotherapy HBV DNA load of $>3 \times 10^5$ copies/mL, and possibly HBeAg positivity [1].

Li *et al.*, in this issue of the journal, present an analysis of 19 patients who developed presumed HBV-related hepatitis following rituximab-containing chemotherapy, in an effort to identify predictive factors for a fatal outcome [18]. Five of the 19 analyzed cases occurred despite lamivudine prophylaxis, albeit of suboptimal duration. In total, nine patients died (47%). In univariate analysis, the following factors were associated with fatal outcome: shorter time period between last rituximab dose and HBV flare (median 3 vs. 8 weeks, $p = 0.012$), shorter time between last chemotherapy and the flare (median 3 vs. 15.5 weeks, $p = 0.011$), and higher peak international normalized ratio (INR) ($p < 0.001$) and bilirubin ($p = 0.014$) levels. There were trends toward association with a fatal outcome with HBeAb negativity ($p = 0.057$) and longer time to viral response to treatment ($p = 0.107$), but the study was underpowered with just 19 cases, and the true impact of these variables remains unclear. Two patients developed HBV flare due to YMDD (tyrosine–methionine–aspartate–aspartate) mutant breakthrough while on lamivudine prophylaxis, and both patients died. Notably, two patients developed fatal hepatitis flares after ceasing lamivudine prophylaxis.

It has been unequivocally demonstrated in patients who are HBsAg positive, in a large, prospective trial, that prophylactic lamivudine treatment reduces the risk of HBV reactivation, clinical hepatitis, and severe hepatitis [2]. Additionally, a large meta-analysis [19] has demonstrated an overall 3-year survival benefit of 2.4% when lamivudine prophylaxis is given, with HBV-related mortality falling from 2.5 to 0.1% [19]. However, the use of prophylactic lamivudine raises several issues. First, the optimal duration of prophylaxis is unclear [2], with cases of hepatitis occurring more than 6 months after completion of chemotherapy (Seymour & Thursky, personal communication, June 2010). The European Society for the Study of the Liver (EASL) recommends treatment for 12 months after cessation of chemotherapy [20], but continued clinical monitoring is required even beyond that time. Second, emergence of the lamivudine-resistant YMDD mutation is problematic during prophylactic lamivudine therapy, and increases with duration of lamivudine use. In the non-oncology setting, this occurs in 24% of patients after 1 year. In the setting of prophylaxis during chemotherapy, the development of YMDD mutation is usually associated with breakthrough hepatitis [2]. This is likely to become an even more significant problem in patients treated with rituximab for a prolonged duration, such as 2-year maintenance schedules for the treatment of low-grade non-Hodgkin lymphoma. After 3 years of treatment, a likely duration in that setting, the prevalence of lamivudine-resistant YMDD mutation is 49% [20]. Concern over this has led the EASL to recommend treatment with either tenofovir or entecavir, especially in patients with a high HBV DNA viral load, as these agents are associated with a far lower rate of development of resistant mutants (0.2% and 1.2% for entecavir at 1 and 3 years, respectively) [20]. However, there are no data yet available on their use in the setting of prophylaxis during treatment of hematological malignancies.

In comparison to other trials and case series, the mortality rate in the report from Li *et al.* is extremely high, at 47%. Given that the report comes from a tertiary referral center specializing in liver disease, this may be explained by referral bias, in that only severe cases were referred to their center for treatment and the series is not incidence-based. Nonetheless, this is concerning, particularly as in both their series and in previous reports [1,2] the administration of nucleoside analog therapy after the development of established hepatitis did not alter the clinical course of the disease. This strengthens the case further for the routine use of nucleoside analog prophylaxis.

Fatal HBV reactivation occurred in two patients with resolved hepatitis-B infection (i.e. HBcAb positive, HBsAg negative). It is known that low levels of HBV replication persist in the liver and peripheral blood mononuclear cells in these patients [21,22], and reactivation has occurred in the setting of allogeneic and autologous HSCT [1]. However, this group of patients had previously been considered to be at very low risk of reactivation after chemotherapy. The finding by Yeo and Johnson that rituximab in addition to CHOP led to hepatitis reactivation in 20% of patients (five of 25, one fatal) who were HBsAg negative, compared to none of those patients treated with CHOP alone, is strong evidence for a contributory role of rituximab. Previous [23] and subsequent [24] reports have suggested that the risk of reactivation is lower, placing it between 1 and 2.7%. The true risk/benefit balance of prophylactic strategies for use in this group are not clear; however, given the severity of the complication, even an incidence of 1% would be concerning. The EASL currently recommend close monitoring, with regular HBV DNA level assessment and treatment with a nucleoside analog if HBV DNA becomes detectable. Several studies have shown that HBV DNA levels most often rise prior to alanine transaminase (ALT) rise [1,25]. However, Hsu *et al.* have shown that

although HBV DNA rise most commonly precedes ALT elevation, by a median of 23 days, it may in some cases coincide with, or follow, the development of ALT rise and clinical hepatitis [2]. Thus, even with very frequent HBV DNA monitoring, the prevention of clinical hepatitis will not always be possible. This strategy also requires a high degree of clinical vigilance and laboratory support to achieve the required rapid turnaround of results, and may thus present practical difficulties in implementation. Indeed, Hsu *et al*. recommend testing as frequently as weekly to twice weekly, given that they observed development of ALT elevation as early as only 7 days after DNA rise. The cost effectiveness of this strategy has rightly been questioned [17].

Given the clinical significance in terms of both high mortality rates and interruptions to chemotherapy delivery, with possible deleterious consequences for overall lymphoma outcome, it is clear that the prevention of HBV reactivation is of paramount importance. Patients undergoing chemoimmunotherapy for lymphoma who are HBsAg positive should receive prophylaxis with a nucleoside analog. There is sparse evidence to guide the choice of a specific nucleoside analog. Indeed, most studies in the setting of prophylaxis during cancer treatment have utilized lamivudine. However, given the high cumulative rates of resistance during treatment with lamivudine and the occurrence of fatal breakthrough hepatitis, both in the current series and in others, we concur with the EASL guidelines [20] that tenofovir or entecavir, which have greater potency and lesser potential for the development of resistance, should be used as frontline agents in high-risk patients. The specific risk of developing a YMDD mutation has not been defined for prophylactic therapy with lamivudine in the hematology population. However, patients with a high HBV DNA level and those who are eAg positive or have pre-core mutant disease are likely at higher risk. It is less clear whether entecavir or tenofovir is required in the setting of non-replicative infection (HBsAg positive, HBeAg negative, HBV DNA negative). Additionally, patients who require a longer duration of prophylaxis, such as those receiving maintenance rituximab for 2 years after completion of chemotherapy for low-grade lymphoma, are likely at higher risk. The American Association for Study of Liver Diseases (AASLD) guidelines recommend consideration of entecavir or tenofovir if the intended treatment duration is greater than 12 months [26].

The optimal duration of prophylaxis for these patients is unclear, but given the occurrence of fatal cases of hepatitis in this case series after the cessation of lamivudine, and previous reports of hepatitis flares 6 months after completion of chemotherapy [2], the EASL recommendation of 12 months of nucleoside analog prophylaxis after completion of chemoimmunotherapy seems reasonable. Patients defined as high-risk, such as those with a high baseline HBV DNA level and HBeAg positive disease, often require treatment for their HBV, independent of the need for prophylaxis during their cancer treatment, and decisions should be made accordingly. Indeed, the AASLD recommends that patients with HBV DNA >2000 copies/mL at baseline be treated until standard endpoints for HBV treatment are met—specifically until 6 months after eAg clearance and HBV DNA suppression in eAg positive patients, and until sAg clearance in eAg negative chronic hepatitis (pre-core mutant disease) [26]. These patients have been shown to be at high risk of withdrawal flares when lamivudine treatment is stopped [27].

We feel that patients receiving rituximab-based regimens who are HBcAb negative, but HBsAg positive, should have either very close monitoring, or consideration of nucleoside analog prophylaxis. Given the lack of data, it is not possible to make a strong recommendation between these techniques. In this setting, where HBV DNA levels are very low, lamivudine may be a reasonable choice if nucleoside analog prophylaxis is given, as the propensity for development of resistance is likely to be lower. Given the need for frequent HBV DNA monitoring if prophylaxis is not given, this may also be a more cost-effective strategy.

Lamivudine is well tolerated during chemotherapy and does not lead to any additional toxicity [28]. However, it is important to be aware of potential drug interactions between lamivudine and purine analog chemotherapeutic agents. A clinically significant drug interaction between prophylactic lamivudine given for prevention of hepatitis-B reactivation during cladribine treatment for chronic lymphocytic leukemia (CLL) has been demonstrated [29]. Both are prodrugs and require intracellular conversion, predominantly via the enzyme deoxycytidine kinase (dCK). Lamivudine competitively inhibits the phosphorylation of cladribine, resulting in a loss of clinical efficacy [29]. Another commonly utilized purine analog, fludarabine, which is used in CLL and low-grade lymphomas, is also phosphorylated to an active form by dCK [30]. There are no available data on an interaction between fludarabine and lamivudine, but clinicians should be aware of the potential for loss of chemotherapeutic efficacy when the two are coprescribed. Other antiviral drugs, such as entecavir, also undergo intracellular phosphorylation, but the precise enzymes responsible have not been elucidated. More data are required before precise recommendations can be made for patients with hepatitis B undergoing purine analog-based chemotherapy.

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