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Lymphoma

Hepatitis B Reactivation and Rituximab in the Oncology Practice

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The article explores the use of lamivudine as prophylaxis for rituximab-induced hepatitis B.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. On the basis of disclosed information, all conflicts of interest have been resolved.

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Perform screening for prior hepatitis B viral exposure in all patients with hematologic malignancies who will receive rituximab as part of their therapy.
2. Implement prophylactic antiviral therapy in patients who are positive for hepatitis B and who are being treated with rituximab.
3. Monitor serum viral load and clinical signs of hepatic injury for at least six months following the completion of rituximab treatment in patients who are hepatitis B-sAg positive.

ABSTRACT

Rituximab use in hematology and oncology practice has significantly and positively improved the clinical outcomes in patients with a wide variety of B-cell lymphoproliferative disorders. However, emerging data reveal that there is a risk of viral hepatitis B reactivation in some patients treated with rituximab. Many of these cases result in treatment delays, inferior oncologic outcomes, increased morbidity, and more rarely fulminant hepatic decompensation and death. Indeed, the rituximab package insert and many clinical practice guidelines have been modified to reflect these concerns. The true incidence and mechanism of reactivation are still being elucidated. This article focuses on the current evidence that supports these recently re-

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vised clinical recommendations along with a review of the risk factors for reactivation, suggested monitoring, and preventative interventions. ***The Oncologist*** 2010;15:1113–1121

Introduction

Rituximab (Rituxan®; Genentech, South San Francisco, CA) has transformed the management of malignant B-cell oncology and is increasingly being considered in nonmalignant lymphoproliferative and immune-mediated conditions. This chimeric murine/human monoclonal antibody targets the $CD20^+$ antigen of the surface of normal and malignant B lymphocytes, which is present in up to 95% of B-cell non-Hodgkin's lymphoma (NHL). Tumor cell killing is mediated through the activation of complement-dependent B-cell cytotoxicity and antibody-dependent cellular toxicity. Rituximab is FDA-approved for first-line treatment of diffuse large, B-cell, $CD20^+$ positive NHL in combination with anthracycline-based regimens or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy [1–3] and as first-line treatment of follicular, $CD20^+$ positive, B-cell NHL in combination with CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy [4]. Other indications include treatment for relapsed or refractory, low-grade, or follicular $CD20^+$ positive, B-cell NHL [5–8] and treatment for stable low-grade $CD20^+$, B-cell NHL following a partial or complete response to first-line treatment with CVP [9]. Rituximab is also FDA-approved for use in combination with methotrexate in moderate-to-severe rheumatoid arthritis previously unresponsive to antitumor necrosis factor therapy [10]. Efficacy in other lymphocytic and immune mediated disorders is the source of ongoing investigation [11].

Rituximab is very well tolerated by the vast majority of patients. One quarter of patients receiving rituximab may experience fever, chills, infection, asthenia, and lymphopenia. Serious adverse reactions associated with rituximab are rare but include infusion reactions, mucocutaneous reactions, progressive multifocal leukoencephalopathy, and tumor lysis syndrome. A depletion of B-cells has been shown to occur within the first three doses and can last for up to 9 months following treatment. B-cell recovery begins around 6 months after treatment and levels may return to normal by 12 months [11]. Viral infections such as cytomegalovirus, herpes simplex virus, and varicella zoster virus have been reported up to 1 year after discontinuation of therapy. Of particular note is the potential for reactivation of hepatitis B virus (HBV) in oncology patients, which may lead to an interruption of chemotherapy and pose increased treatment-related mortality [11, 12]. It is this latter complication that is the focus of this review.

Reactivation of Hepatitis B Virus

HBV is a DNA virus belonging to the Hepadnavirus family. It has been estimated to affect more than one third of the global population, comprised of up to 400 million chronic carriers of infection [12–16]. Infection can result in a variety of clinical conditions ranging from a transient, asymptomatic state to progressive jaundice and fulminant hepatic decompensation. Patients with underlying cirrhosis are at an increased risk for severe symptoms and mortality [12].

According to the American Association for the Study of Liver Diseases (AASLD) Chronic Hepatitis B Guidelines, reactivation of hepatitis B is defined as the reappearance of active necroinflammatory disease of the liver in a person

Table 1. Definitions of hepatitis B virus states and patient serologies

	HBsAg	HBeAg	HBeAb	ALT/AST	Histology	HBV DNA
Inactive carrier	Positive >6 mo(s)	Negative	Positive	Normal	Absence of hepatitis, minimal fibrosis (necroinflammatory score <4)	<2,000 IU/mL
Resolved (known positive HBsAb in absence of vaccination or HBcAb positive)	Negative	Negative	Positive	Normal	Absence of hepatitis, scant fibrosis	Undetectable
Reactivation	Positive >6 mo(s)	Negative	Positive	Elevated or fluctuating	Variable fibrosis (necroinflammatory score >4)	Moderate or fluctuation (>2,000 IU/mL)

Abbreviations: HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen.

Table 2. Summary of trials investigating incidence of HBV reactivation after rituximab treatment

Trial	Patient population	Serology	Total patients (*n*)	HBV + patients receiving rituximab (*n*)	Incidence of reactivation (%)	Median time to reactivation (mo(s))	Comments
Yeo et al. [21]	Lymphoma	80 HBsAg (−): 46 HBcAb (+), 34 HBcAb (−)	104	37	5/21 (24%)	3.3 (2–37)	(a) 1 patient had reactivation after the 5th cycle of therapy; (b) 3 patients developed reactivation after completion of R-CHOP
Hui et al. [23]	Lymphoma	All patients initially HBsAg (−)	244	7/8, de novo seropositivity during study	8/244 (3.2%)	4.6 (3–7)	(a) 3 patients developed fulminant hepatic failure: 2 recovered, 1 death; (b) Rituximab plus a steroid-containing regimen was the only independent risk factor associated with de novo HBV-related hepatitis after treatment with chemotherapy (RR 13.8; 95% CI: 2.77–68.30; $p = 0.001$)
Hanbali and Khaled [24]	Rituximab recipients	12 HBsAg (−), HbsAb (+), HBcAb (+); 6 HBsAg (−), HBsAb (−), HBcAb (+); 8 HBsAg (−), HBsAb (NA), HBcAb (+); 6 HBsAg (+), HBsAb (variable), HBcAb (variable)	456	32/32	11/32 (34%)	6.2 (except for 2 patients who developed events at 21 and 36 mo(s))	(a) HBV reactivation defined as any patient who experienced acute liver events including elevations of liver enzymes, biopsy confirmed hepatitis or necrosis, hepatic encephalopathy, or viral DNA replication; (b) HBsAg (+) represented the strongest correlation in patients who developed acute liver events 4/6 (66%)
Koo et al. [25]	Lymphoma	HBsAg (−), HBcAb (+)	233	46/80	1/46 (2.2%)	2	Fatal reactivation in 1 patient
Metzler et al. [26]	Rituximab recipients	HbsAb (+), HBcAb (+)	258	20/20	3/20 (15%)	3–10.6	(a) 78 patients had no record of HBV testing; (b) 2 patients became HBsAg positive and HBsAb negative; (c) 1 patient remained HBsAb positive and HBcAb positive; (d) no HBV-related deaths
Vega et al. [20]	Rituximab recipients	Hepatitis B or hepatitis C positive serology	635	49/49	3/49 (6%)	NR; median follow-up of 25 mo(s)	Co-infection with HBV and HCV resulted in a significant increase in severe liver events

Abbreviations: (−), negative; (+), positive; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; NR, not reported.

known to have (1) an inactive hepatitis B surface antigen (HBsAg) carrier state (persistent HBV infection of the liver without significant, ongoing necroinflammatory disease) or (2) resolved hepatitis B (previous HBV infection without further virologic, biochemical, or histological evidence of active virus infection or disease) [17]. Thus, HBV reactivation can occur in both inactive carriers as well as those with resolved HBV infection. However, viral reactivation rates appear highest in those with HBsAg positive serologies, especially those with active HBV replication (HBV DNA positive in serum). Those with the lowest risk of reactivation are patients positive for hepatitis core antibody (HBcAb) with previous exposure and no evidence of a chronic carrier state (HBsAg negative) [17, 18]. Table 1 summarizes HBV reactivation definitions and serologies.

In 2004, the U.S. Food and Drug Administration notified healthcare professionals about reports of fulminant HBV, hepatic failure, and death in patients with hematologic malignancies receiving rituximab [11]. Reactivation of HBV due to the immunosuppressive actions of rituximab has been reported in both HBsAg positive carriers and those with chronic HBV infection [13]. As a result of increasing clinical attention to this matter and recent reports of HBV reactivation, the American Society of Clinical Oncology (ASCO) has recently issued a Provisional Clinical Opinion on HBV screening in patients receiving treatment of malignant diseases [19].

The possible relationship between rituximab and hepatitis B may be explained by the depletion of B cells, which serve critical roles in both T-cell and antibody-mediated immunity in HBV infection [12]. Reactivation of HBV typically occurs between 4 months after initiation of and 1 month after completion of rituximab therapy [11]. The overall incidence of reactivation with use of rituximab is unclear, but ranges from 2% to 35% of patients (Table 2) [20–26]. There is a paucity of published data on hepatitis B reactivation in patients receiving rituximab for nonmalignancy indications, such as for the treatment of graft versus host disease or idiopathic thrombocytopenic purpura.

The addition of rituximab to CHOP (R-CHOP) chemotherapy in diffuse large B-cell NHL (DLBCL) has demonstrated an increase in response rate, event-free, and overall survival [27]. This has become a well-established standard of care [28]. However, the addition of rituximab has also

Table 3. Hepatic metabolism and excretion of drugs routinely used with rituximab

Class	Drug	Metabolism	Excretion
Alkylating agents	Bendamustine	Hepatic via CYP1A2 to active (minor) metabolites	Feces (~90%); urine (1%–10%)
	Carmustine	Rapidly hepatic; forms active metabolites	Urine (60%–70%); lungs (6%–10% as CO_2)
	Chlorambucil	Hepatic to active (major) metabolite	Urine (15%–60%)
	Cyclophosphamide	Hepatic to active metabolites	Urine (<30% as unchanged drug)
	Ifosfamide	Hepatic to active and inactive metabolites	Urine based on dose: high dose (5000 mg/m^2): 70%–86% (61% as unchanged drug); low dose (1600–2400 mg/m^2): 12%–18% as unchanged drug
	Thiotepa	Hepatic to active (major) metabolite	Urine (as metabolites and unchanged drug)
Anthracenedione	Mitoxantrone	Hepatic; pathway not determined	Feces (25%); urine (6%–11%; 65% as unchanged drug)
Anthracyclines	Doxorubicin	Hepatic to active metabolite	Feces (~40%–50% as unchanged drug); urine (~5%–12% as unchanged drug and metabolites)
Antibiotic antineoplastic agents	Bleomycin	Several tissues including hepatic; GI tract, skin, pulmonary, renal, and serum	Urine (50%–70% as active drug)
Antimetabolites	Gemcitabine	Intracellularly by nucleoside kinases to active metabolites	Urine (92%–98% as inactive metabolite) and feces (<1%)
	Methotrexate	Degraded by intestinal flora	Urine (44%–100%); feces
Corticosteroids	Dexamethasone	Hepatic	Urine and feces
	Hydrocortisone	Hepatic	Urine
	Prednisolone	Primarily hepatic	Urine
Podophyllotoxin derivative	Etoposide	Hepatic	Urine (42%–67%; 8%–35% as unchanged drug) within 24 hours; feces (up to 44%)
Taxanes	Paclitaxel	Hepatic via CYP2C8 and 3A4 to metabolites	Feces (~70%, 5% as unchanged drug); urine (14%)
Vinca alkaloids	Vinblastine	Hepatic to active metabolite	Feces (95%); urine (<1% as unchanged drug)
	Vincristine	Hepatic	Feces (~80%); urine (<1% as unchanged drug)

Adapted from Lexi-Comp Online. Available at http://www.lexicomponline.com. Accessed December 18, 2009, with permission.

been shown to increase the risk of HBV reactivation both in inactive carriers and those with resolved HBV. Yeo et al. [21] examined the risk of HBV reactivation in a prospective study where newly diagnosed diffuse large B-cell, CD20$^+$ positive NHL patients were observed for HBV reactivation. This was defined as an increase in HBV DNA levels of tenfold or more compared to baseline or an absolute increase of HBV DNA levels >1,000 $\times$ 10^6 genomic equivalents per mL in absence of systemic infection with alanine transaminase (ALT) elevation during and for 6 months after anticancer therapy. Of the entire cohort of diagnosed CD20 positive DLBCL, 80 of 104 patients were negative for HBsAg at baseline. However, 46 of these HBsAg negative patients were positive for the antibody to hepatitis B core antigen (anti-HBc), indicating resolved prior HBV infection. Reactivation of hepatitis B occurred in 5 of 21 (24%) of these patients when treated with R-CHOP for 5–8 cycles. None of the remaining 25 (anti-HBc positive) patients treated with CHOP alone developed reactivation following treatment. Of the 5 patients who developed HBV reactivation, 3 patients had resolution of hepatitis with antiviral medication and 1 patient died of hepatic failure despite receiving antiviral medication, whereas another patient had spontaneous resolution of HBV without antiviral medica-

Table 4. Risk factors associated with hepatitis B virus reactivation in oncology patients

Male	Lymphoma
HBeAg seropositivity	Use of anthracyclines and/or steroids
Second- or third-line chemotherapy	Detectable or high pre-chemotherapy HBV DNA
Younger age	Pre-chemotherapy ALT elevation
Rituximab	Breast cancer

Abbreviations: ALT, alanine transaminase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

tion. Time to reactivation from the last chemotherapy cycle ranged from 19 to 170 days. Peak ALT and peak HBV DNA levels ranged from 362 to 2,110 U/L and from 4,820 to 231,598 copies/mcL, respectively [21]. Vega and colleagues showed that 21 out of 49 (43%) patients with a positive hepatitis serology (HBsAb positive/HBcAb positive, HBcAb positive, or HBsAg positive) treated with rituximab developed liver events (defined as elevation of liver transaminases $>$ 2 times the upper normal limit, new or worsening signs of cirrhosis, necrosis of the liver, and death secondary to liver failure viral reactivation). Of the 27 HBV positive patients, 11% developed viral reactivation resulting in death secondary to liver failure [20]. In a review of 97 cases of HBV reactivation during or after chemotherapy, 9 of 81 (11%) lymphoma patients had received rituximab as part of their therapy [13].

The mortality rate associated with viral reactivation has ranged from 4% to 60% [13]. Most deaths occur primarily because of acute liver failure [15]. Morbidity may be underestimated and falsely attributed to systemic chemotherapy. Liver dysfunction from HBV reactivation may result in increased systemic toxicity of chemotherapy agents that are hepatically metabolized and excreted (Table 3) [29]. Diagnostic parameters have not been established for HBV reactivation nor has there been specific grading of the associated hepatic decompensation [30]. Clinical signs and symptoms related to HBV reactivation may be subtle. A sudden increase in aminotransferase (ALT $>$5 times the upper limit of normal or $>$3 times above baseline) may be indicative of reactivation (i.e., hepatic flare), but can be seen in a variety of conditions related and unrelated to the oncologist's purview. Serum viral load increases about 2 to 3 weeks before ALT levels rise. Thus, rising viral load levels may serve as an important monitoring parameter prior to development of clinical sequelae. However, viral DNA levels may be declining or be undetectable when hepatic flare is clinically apparent. Hepatic flares may also be associated with an abnormal serum bilirubin, albumin, alkaline phosphatase, and prothrombin time, an increase in serum immunoglobulin M (IgM) anti-HBc and alpha fetoprotein levels, and encephalopathy [31, 32]. In addition to rituximab use, risk factors for HBV reactivation in oncology patients include male sex, use of anthracyclines, corticosteroid treatment, hepatitis B e antigen (HBeAg) seropositivity, and pre-existing abnormalities in liver function tests (Table 4) [12]. Hepatic flare can consequently lead to interruptions in delivering curative chemotherapy, lasting as long as 100 days [33]. Such delays in chemotherapy may result in a decreased disease-free and overall survival [15]. Even newly approved antineoplastic agents that target $CD20^+$ lymphocytes including ofatumumab (Arzerra®, FDA approved October 2009; GlaxoSmithKline, Research Triangle Park, NC) carry warnings about HBV reactivation and recommend screening patients prior to use [34].

Antiviral Prophylaxis

The use of antiviral medication to reduce viral replication and to prevent progression to worsening hepatitis has been extensively studied in the nononcology patient population. Lamivudine (Epivir®, Epivir-HBV®; GlaxoSmithKline), an oral nucleoside analogue, has been shown to reduce HBV viral load and improve liver injury in patients with chronic HBV [13–15]. Epivir® is FDA-approved for the treatment of HIV-1 infection as part of a multidrug regimen with at least three antiretroviral agents and is dosed to treat HIV-1 and not HBV [35–38]. Epivir-HBV® is FDA-approved for the treatment of chronic HBV associated with evidence of viral replication and active liver inflammation [39–42].

Lamivudine has been extensively studied as prophylaxis in the prevention of HBV reactivation during chemotherapy in HBsAg positive patients (Table 5) [14, 15, 43–66]. Loomba and colleagues published a systematic review of 14 trials (total of 275 patients) showing that lamivudine use significantly reduces the risk for both HBV reactivation and HBV-related hepatitis by nearly 80%. No patient with HBV reactivation died due to hepatic failure in the lamivudine prophylaxis arm in any of the studies included in this review. Control groups showed a higher disruption of chemotherapy and an increased rate of cancer-related and all-cause mortality [14]. Another review of 10 prospective trials, which included 5 studies not analyzed in the earlier review, showed a lower rate of hepatitis among subjects receiving lamivudine (16 of 173, 9.2%) compared with subjects not receiving lamivudine (63 of 116, 54%). Of patients receiving prophylaxis, 8.7% (15 of 173) developed HBV reactivation compared to 37% (43 of 116) without prophylaxis. Statistical significance and risk reduction were not assessed in this second review; however, none of the trials

Table 5. Summary of trials investigating lamivudine prophylaxis[a] for chemotherapy-related HBV reactivation

Study	Duration of prophylaxis		Incidence of HBV reactivation			Comments and other outcomes
	Start (relative to chemo initiation)	Stop (relative to chemo discontinuation)	Lamivudine group (%)	Control group (%)	Relative risk reduction (95% CI)	
Randomized controlled trials						
Jang et al. [43]	Day 0	12 mo(s)	1/36 (2.7%)	15/37 (40.5%)	0.07 (0.01–0.35)	(a) Less disruption of chemotherapy; (b) all-cause mortality decreased
Lau et al. [44]	Day −7	1.5 mo(s)	0/15 (0%)	8/15 (53.3%)	0.00 (0.00–0.39)	All-cause mortality decreased
Prospective cohorts						
Cardinale et al. [45]	Day −7	6 mo(s)	0/4 (0%)	NR		No HBV reactivation reported
Dai et al. [46]	Day −7	1 mo(s)	1/6 (16.7%)	NR		
Dai et al. [47]	Day −7	1 mo(s)	0/11 (0%)	5/9 (55.5%)	0.00 (0.00–0.61)	(a) All-cause mortality decreased; (b) historical control
el-Sayed et al. [48]	Day 0	Same time	0/5 (0%)	NR		Lamivudine dose: 3 mg/kg per day
He et al. [49]	Day −7	median 5.5 mo(s); range 2–16)	1/29 (3.4%)	NR		(a) 4/29 (13.8%) developed hepatitis unrelated to HBV reactivation; (b) 1/29 (3.5%) had a delay in chemotherapy; (c) reactivation resolved with re- administration
Hsu et al. [50]	Day 0	2 mo(s)	3/26 (11.5%)	14/25 (56%)	0.21 (0.04–0.59)	Historical control
Hui et al. [51]	Day −7	3 mo(s)	11/46 (23.9%)	NR		
Idilman et al. [52]	Day 0	12 mo(s)	0/8 (0%)	5/10 (50%)	0.00 (0.00–0.79)	
Jia and Lin [53]	NR	NR	1/8 (12.5%)	7/8 (87.5%)	0.14 (0.01–0.67)	Historical control
Rossi et al. [54]	Day 0	1 mo(s)	1/20 (5%)	NR		
Shibolet et al. [55]	Day 0	7 mo(s)	0/9 (0%)	2/5 (40%)	0.00 (0.00–1.31)	Historical control
Vassiliadis et al. [56]	Day −19	Ongoing	0/10 (0%)	NR		
Yeo et al. [57]	Day −7	2 mo(s)	3/65 (4.6%)	47/193 (24.4%)	0.19 (0.04–0.52)	(a) Less disruption of chemotherapy; (b) historical control
Yeo et al. [58]	Day −7	2 mo(s)	2/31 (6.5%)	19/61 (31.1%)	NR	(a) Less disruption of chemotherapy; (b) historical control
Yeo et al. [59]	Day −7	2 mo(s)	0/16 (0%)	6/21 (28.6%)	0.00 (0.00–0.75)	(a) Less disruption of chemotherapy; (b) historical control
Retrospective cohorts						
Leaw et al. [60]	Day 0	1 mo(s)	0/11 (0%)	17/53 (32%)	0.00 (0.00–0.86)	All-cause mortality decreased
Lee et al. [61]	NR	NR	1/11 (9%)	17/20 (85%)	0.11 (0.01–0.46)	Less hepatic failure-related death
Lim et al. [62]	Day −7	Same time	0/16 (0%)	7/19 (36.8%)	0.00 (0.00–0.56)	All-cause mortality decreased
Nagamatsu et al. [63]	Day −28	Same time	0/8 (0%)	6/9 (66.7%)	0.00 (0.00–0.66)	All-cause mortality decreased
Ozguroglu et al. [64]	NR	NR	0/4 (0%)	8/12 (67%)	NR	Reactivation (8): 2 treated with lamivudine, 4 untreated died with liver failure, 2 died secondary to NHL treatment delay
Persico et al. [65]	Day 0	2 mo(s)	0/3 (0%)	12/21 (57%)	NR	Reactivation (12): 9 treated with lamivudine, 3 untreated died with liver failure
Yokoyama et al. [66]	NR	NR	1/8 (12.5%)	NR	NR	No significant difference HBsAg (+) versus HBsAg (−) patients in overall and 2-yr progression-free survival

[a]Dose of lamivudine used in all studies was 100 mg/day except where otherwise noted.
Abbreviations: HBsAg, hepatitis B surface antigen; NR, not reported; (+), positive; (−), negative.

reported discontinuation of chemotherapy or withdrawal due to lamivudine toxicity [15]. Both reviews included studies with mostly inactive carriers (patients with HBsAg seropositivity and the highest risk of reactivation).

Lamivudine is typically very well tolerated, although it can be associated with headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea, and cough. Serious adverse reactions are rare and include lactic acidosis, severe hepatomegaly with steatosis, and pancreatitis. There have also been reports of severe acute exacerbations of hepatitis B and hepatic decompensation in patients co-infected with HIV-1 and hepatitis C, likely due to the development of HBV drug resistance [67]. The incidence of resistance to lamivudine can be as high as 20% after the first year of administration in patients with active HBV replication due to a mutation in the tyrosine-methionine-aspartate-aspartate

motif of the HBV DNA polymerase gene (YMDD mutation) [16, 68, 69]. The development of drug resistance may be particularly relevant for patients who are likely cured from their NHL or other lymphoproliferative condition and have long-term needs for viral suppression due to active HBV infection.

Clinical Recommendations

In July 2009, the National Comprehensive Cancer Network (NCCN) NHL Guidelines were updated to include recommendations on rituximab-associated viral reactivation. Routine serologic testing for prior HBV exposure via surface antibody/antigen and core antibody/antigen is now recommended for patients with B-cell NHL. In addition, whereas a recent Provisional Clinical Opinion by the American Society of Clinical Oncology (ASCO) found that there was not enough evidence to determine the benefits of routine screening for chronic HBV infection in cancer patients about to undergo cytotoxic chemotherapy, there are consistent recommendations that screening should be considered in those at high risk for HBV reactivation, particularly those patients who will receive rituximab as part of their therapy [19]. Known HBV carriers should be monitored closely for viral reactivation via serial serum viral loads during therapy and for at least 6 months following completion [28]. According to the clinical guideline recommendations, antiviral therapy should be considered as prophylaxis when treating HBV positive patients with rituximab [28, 70].

Unfortunately, there are few specific recommendations for the optimal dose and duration of prophylaxis at this time. The majority of relevant studies administered 100 mg of lamivudine by mouth daily until 6 months after the completion of chemotherapy. Lamivudine use during and for 6 months after completion of chemotherapy has also been recommended in recent guidelines published by the American Association for the Study of Liver Diseases [14]. A longer duration of prophylaxis may be necessary in patients with higher initial levels of HBV DNA or those on maintenance rituximab [12]. Furthermore, HBV reactivation may increase following the withdrawal of lamivudine prophylaxis [15]. Due to the high risk of developing resistance to lamivudine with long-term therapy, other antiviral drugs should be considered in those patients who will require suppressive therapy beyond chemotherapy prophylaxis. Alternative antiviral agents like entecavir (Baraclude®; E.R. Squibb & Sons, L.L.C., New Brunswick, NJ), adefovir dipivoxil (Hepsera®; Gilead Sciences, Inc., Foster City, CA), and tenofovir disoproxil fumarate (Gilead Sciences, Inc.) may ultimately be preferred due to increased antiviral potency and decreased rates of current drug resistance [12]. Ongoing studies will help to validate these recommendations and resolve issues related to the heterogeneity of patient populations (i.e., inactive carriers versus resolved HBV infection), variable initiation, duration and follow-up of treatment, comparison with other antiviral agents, and comparison between hematologic, lymphoma, and nononcologic rituximab use.

Conclusions

HBV reactivation related to rituximab use is associated with increased morbidity and mortality in oncology practice. Serologic screening for prior HBV exposure or active infection should be performed prior to rituximab use in patients with hematologic malignancies. Antiviral prophylaxis should be started before chemotherapy and continued for at least 6 months following completion of all treatment for patients who are at high risk with HBsAg seropositivity and low HBV DNA $<$2,000 IU/mL. Evidence to support prophylaxis in patients with resolved HBV infection is limited. Lamivudine can be used if the duration of treatment is $<$12 months, whereas alternative antiviral agents (tenofovir or entecavir) may be preferred if anticipated treatment may last longer than 12 months. Prophylaxis should be continued until treatment endpoints are reached for reactivation of hepatitis B in patients with HBV DNA $>$2,000 IU/mL (Table 1) [17–19, 28]. Serum viral load should be monitored in those who are HBsAg positive, as well as close clinical monitoring for potential hepatic injury. Consultation with hepatology or infectious disease colleagues should also be considered, especially in those with active viral replication. If HBV reactivation of hepatitis B occurs, rituximab and any concomitant chemotherapy should be discontinued [28]. Although HBV reactivation may be self-limited with supportive care, antiviral therapy should be initiated as soon as possible (if not already used as prophylaxis) to prevent rapid progression to hepatic decompensation. Further clinical investigation is needed to answer many clinical questions including determining the optimal dose and duration of prophylaxis and establishing the safety of resuming rituximab after prior HBV reactivation.

Author Contributions

Conception/Design: Thomas J. George, Kourtney LaPlant, Jeryl Villadolid
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